Muscle Coordination Contributes to Function after Stroke; Proprioception Contributes to Control of Posture, Movement

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MUSCLE COORDINATION CONTRIBUTES TO FUNCTION AFTER STROKE; PROPRIOCEPTION CONTRIBUTES TO CONTROL OF POSTURE, MOVEMENT

by

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ABSTRACT

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More than half of stroke survivors experience persistent upper extremity motor impairments that can negatively impact quality of life and independence.
Effective use of the upper extremity requires coordination of agonist/antagonist muscle pairs, as well as coordination of multiple control actions for stabilizing and moving the arm. In this dissertation, I present three studies in which I recorded isometric torque production, single joint movement and stabilization, and clinical measures of function and impairments after stroke to evaluate the extent to which changes in coordination of agonist/antagonist muscles and of sequential control actions contribute to deficits after stroke. In Aim 1, I quantified the extent to which stroke-related deficits in the coordination of agonist/antagonist muscle pairs degraded the ability to generate, maintain, and relax cued torques about the elbow. Participants who survived stroke (SP) and neurologically intact participants (NI) performed pursuit tracking of step-changes in isomeric torque targets to investigate coordination of activation magnitude in elbow agonist/antagonist muscle pairs. SP had marked hypertonia of the primary flexor muscles, which led to increased compensatory activity in the primary extensor muscles. These stroke-related deficits of muscle coordination degraded ability to generate, maintain, and relax cued torque production. In Aim 2, SP and NI performed sequential combinations of elbow stabilization and movements to investigate impairments in execution and coordination of these fundamental control actions. Impaired proprioception in SP was associated with increased impairments in stabilizing the arm against a perturbation compared with SP with intact proprioception. Surprisingly, SP with intact proprioception had greater impairments when moving than did SP with impaired proprioception. These results support the supposition that deficits of somatosensation can differentially impact neural control of limb stabilization and movement. Aim 3 used correlation and forward regression to compare deficits of muscle coordination (Aim 1) and control (Aim 2) to one another in order to quantify the extent to which each could explain deficits of motor function after stroke. Taken together, the three studies revealed that stroke-related deficits in coordination timing and magnitude of muscle activation impact clinically-measured function, and that somatosensory deficits can differentially impair neuromotor stabilization and movement control.

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CHAPTER 1: RATIONALE AND SPECIFIC AIMS

Rationale and Hypothesis

Persistent impairment of the more-impacted upper extremity is a reality of life for the majority of survivors of stroke (Winstein et al. 2016). The most common upper extremity impairment is paresis, weakness thought to be driven in part by lost descending control (Lundy-Eckman 2007). Paresis can contribute to loss of function and disuse of the more-impacted upper extremity which can impact stroke survivors' ability to perform activities of daily living, such as brushing one's teeth or toileting, or even one's ability to live independently if activities such as driving or performing work responsibilities are sufficiently impacted (Winstein et al. 2016). In this Dissertation, we hope to elucidate some of the factors we believe to underlie loss of function and motor impairment after stroke. Specifically, we study stroke-related changes in control and coordination of agonist/antagonist muscle pairs, stroke-related changes in fundamental control actions used to stabilize and move the arm, and how stroke impacts sequential coordination of these control actions. We then relate these measures to clinical measures of motor function and impairment in survivors of stroke.

Clinical measures of function and impairment after stroke are multifaceted tools that quantify several aspects of impairment. One such measure of impairment, the Fugl-Meyer Assessment, evaluates reflex abnormalities, the ability to move in and out of muscle synergies, and voluntary wrist and hand movement (FM_M, Fugl-Meyer et al. 1975). A measure of function, the Chedoke Arm and Hand Activities Inventory, evaluates performance of bilateral arm activities of daily living such as filling a glass of

water or cutting food (CAHAI, Gowland 1993). While these measures are clinically useful for staging and tracking recovery, the specific, stroke-related deficits underlying these broad measures remains unclear. Many research groups have sought to employ well-controlled laboratory-based assessments to fill this knowledge gap by characterizing how stroke-related impairments impact specific aspects of neuromotor control, as well as how those control deficits impact motor function.

Well-organized coordination of agonist/antagonist muscle pairs in time and magnitude is crucial for creating controlled torque at a joint, such as that used to steady the arm against the force of gravity during movement. However, there are many reported deficits in muscular control after stroke that interfere with this type of muscle coordination and can decrease success of movements. Deficits include abnormalities in timing of contraction onset and/or termination (Chae et al. 2002, Kautz and Brown 1998), poor coupling of muscle activation patterns with a task objective (target tracking), and excessive muscle activation (Canning et al. 2000), which can lead to impairment in torque production (Kamper and Rymer 2001). Additionally, these abnormalities may be exacerbated at certain joint angles, such as when the arm is positioned such that a muscle is stretched beyond its static stretch reflex threshold, which is often within the range of achievable motion in survivors of stroke and can cause constant activation in the stretched muscle (Levin et al. 2000).

There is evidence to suggest that a single point-to-point reach is actually controlled by a series of distinct neural mechanisms enacted sequentially (Humphrey and Reed 1983, Sheridan 1984, Schaal and Atkeson 1998, Sainburg et al. 1999). First, movement control is thought to consist of a *feedforward controller* that initiates

movement, and then a proprioception-based online *feedback controller* that corrects the trajectory as the movement occurs. As the movement approaches its end location a *postural controller* is thought to be used to terminate movement (Sainburg et al. 1999, Scheidt and Ghez 2007, Ghez et al. 2007). In healthy point-to-point reaching, these three control actions are executed sequentially, but overlapping in time (thus blending the control phases into one another) and producing a smooth and accurate targeted movement. However, these control actions appear to be differentially impacted by stroke (Scheidt and Stoeckmann 2007, Schaefer et al. 2009).

The studies described in this Dissertation quantify kinematic coordination of sequential control actions and coordination of activation in agonist/antagonist muscle pairs in participants with unilateral stroke (SP) and compare them to coordination patterns used by neurologically intact (NI) participants. The coordination deficits observed in the SP are then used to quantify the extent to which these deficits can explain limitations in function and motor impairments observed after stroke. *We test the hypotheses that deficits in coordinating timing and magnitude of agonist/antagonist muscle activations at the elbow and deficits in coordinating sequential stabilization and movement control actions contribute significantly to deficits in motor function and motor impairment after stroke.*

Aim 1: Quantify the extent to which joint angle-dependent deficits in agonist/antagonist muscle coordination degrade the ability to produce controlled, goal-directed changes in elbow joint torque after stroke.

Prior work has examined isometric torque production tasks at the more affected elbow (Canning et al 1999; Chang et al. 2013; McCrea 2003) and wrist (Chae et al. 2002)

in order to characterize the impact of stroke on aspects of neuromuscular coordination including maximal torque production (Chae et al. 2002, McCrea 2003), rates of torque development and reduction (Canning et al. 1999, McCrea 2003), spontaneous discharge of motor units (Chang et al. 2013), and the degree of co-activation (Chae et al. 2002) during torque production without the potential confound of limb motion and the abnormal velocity-dependent reflex responses it can elicit. Findings of these experiments include marked weakness and slow rates of torque development (McCrea et al. 2003, Canning et al. 1999), in addition to delay in the initiation and termination of muscle activation (Chae et al. 2002), as well as sustained increases in spontaneous discharges of motor units after voluntary activation (Chang et al. 2013)

Additionally, arm position has been observed to contribute significantly to muscle function and torque production after stroke. Levin and colleagues describe studies designed to characterize deficits in the regulation of stretch reflex thresholds - a neuromuscular mechanism believed to underlie hemiparesis after stroke (Levin et al., 1997) and other brain injuries (Levin et al., 2000). In NI participants, there is no part of the achievable range of motion in the arm that will spontaneously trigger stretch reflex. In 11/12 SP however, Levin and colleagues (2000) found that static flexor stretch reflexes were spontaneously triggered (consequently giving rise to involuntary hypertonia) when the arm was placed in joint angles within the physiological range of motion. Similar effects were observed in the extensors of approximately one third of SP. These abnormal stretch reflexes limited the range in which reciprocally organized muscle activity could be generated. They were also related to reductions in the maximal flexor and extensor torques that the hemiparetic participants were able to produce when the functional agonist

muscle was lengthened. Unfortunately, no attempt was made to link these results to motor function, thus leaving unresolved the question of how joint angle-related deficits of motor control might contribute to deficits of motor function post-stroke.

In the first experiment, NI and SP participants completed a series of isometric step-torque tracking tasks at the elbow, alternating between matching moderate flexion or extension torque targets and a relaxed (no torque) target. Each task was repeated at three elbow joint angles to allow testing with each muscle shortened, neutral, and lengthened. Kinetic performance and electromyograms (EMG) were used to calculate measures of torque production and coordination of agonist/antagonist muscle activation during relaxation and torque generation. These measures were used to quantify differences in agonist/antagonist muscle coordination and torque production between SP and NI. They then were used to model motor function after stroke as measured by CAHAI and synergy/strength-based motor impairment as measured by FM_M. *We tested the hypothesis that position-dependent deficits of coordination of agonist/antagonist activation – and any resulting constraints on elbow joint torque production – explain significant variance in motor impairment and deficits of motor function after stroke.*

Aim 2: Quantify the extent to which stroke impairs control and coordination of limb stabilization and movement.

Reaching, though a familiar behavior, is far from simple. As previously mentioned, a single targeted point-to-point reach consists of at least three distinct control actions that are sequentially executed with some overlap to produce smooth and accurate reaches. Studies explicitly seeking to test differential impacts of stroke on stabilization and movement control actions have found that after stroke, these control actions adapt

differently from one another to visuomotor perturbations (Schaefer et al. 2009), and that proprioceptive deficits are associated with deficits in final position control (Scheidt and Stoeckmann 2007). Observations by other groups studying reaching impairments after stroke, while not explicitly designed to test for deficits in control actions, have identified segmented reaching, i.e., a loss of movement smoothness after stroke, and inaccuracy in achieving the final desired hand position and thus are suggestive of the types of control impairments that might be expected (Cirstea and Levin 2000, Dipietro et al. 2009, Kamper et al. 2002, Krebbs et al. 1999, Levin 1996, McCrea et al. 2005, Roby-Brami et al. 1997, Rohrer et al. 2002, Rohrer et al. 2004, Trombly 1992).

In order to isolate these control actions to the greatest extent possible, we simplified reaching to a single-joint task about the elbow. This choice allowed us to study the coordination of sequential stabilization and movement control actions in a controlled manner. In this experiment, SP and NI performed a series of targeted, point-to-point elbow movement tasks with the initial and final conditions perturbed by the presence or absence of an adjacent stabilization task. Baseline performance of stabilization and movement control actions was quantified for SP and NI. Then, measures of sequential-task coordination were calculated using performance in the composite stabilization/movement conditions. Finally, these measures of control and sequential coordination were used in an attempt to model function as measured by the CAHAI and impairment as measured by FM_M. *I tested the hypothesis that deficits of coordination between sequential limb stabilization and limb movement control actions correlate significantly to motor impairment and deficits of motor function after stroke.*

Aim 3: Quantify the extent to which stroke-related deficits in coordination of sequential stabilization and movement control actions, and coordination of activation in agonist/antagonist muscle pairs, account for decreased functional ability as measured by the Chedoke Arm and Hand Activities Inventory and motor impairment as measured by the upper extremity portion of the Fugl-Meyer Assessment.

The experiments described above were designed to quantify the extent to which stroke-related deficits of agonist/antagonist muscle coordination degrade the ability to produce controlled, goal-directed changes in elbow joint torque (Aim 1), as well as the impact of stroke on stabilization and movement control actions, and finally, the coordination of these actions when enacted sequentially (Aim 2). The final analyses were designed to compare outcome measure from Aim 1 and Aim 2 to one another to evaluate the extent to which each deficit could account for decreased functional ability and motor impairments in the upper extremity after stroke.

Analyses in this Aim were restricted to SP. First, we tested for correlations between upper extremity function and impairment, and clinical and research measures of specific somatosensory, physical, and mild cognitive impairment; measures of agonist/antagonist muscle coordination from Aim 1 and Aim 2; and measures of coordination of sequential stabilization and movement control actions from Aim 2 to quantify the extent to which these measures were related. Next, we used forward regression to quantify the extent to which these measures could account for differences in clinical function and motor impairment in the upper extremity in our cohort of SP. *We tested the hypothesis that coordination of elbow flexors and extensors, and coordination of sequential stabilization and movement control actions, account for significant variability in clinically measured motor function and impairment after stroke.*

The experiments described in this Dissertation characterized differences in coordination of muscle activity in an agonist/antagonist pair for controlled torque production and coordination of sequentially executed control actions in SP and NI participants and used these measures to model motor function and impairment post-stroke. Our findings in Aim 1 support and expand our knowledge of changes in coordination of agonist/antagonist muscle pairs in the upper extremity after stroke and their implications on torque production at the elbow. Our findings in Aim 2 expand knowledge of the differential impacts of stroke on stabilization and movement-control as well as the impact of stroke on sequential coordination of these control actions, and propose a mechanism for observed differences in control that complements and expands current thinking in the field. Finally, by quantifying the impact that these coordination deficits have on functional deficits after stroke, we advance our understanding of factors that may contribute to motor function after stroke.

CHAPTER 2: BACKGROUND

Prevalence of motor deficits after stroke

Stroke affects motor control in numerous ways. Damage to descending neuromotor systems can result in loss of inhibitory control which can manifest in spasticity, abnormal patterns of muscle activation, and disability in performing selective movements (Bobath 1990). Loss of range of motion, dexterity, and muscle weakness are also common motor outcomes of stroke (Kamper et al. 2002, Trombly 1992). In addition to motor impairment, sensory impairment of proprioception and light touch are also frequently reported (Brain 1956). These deficits can impair motor function, which requires both efferent commands and afferent sensation (Twitchell 1954). This project is motivated by the belief that clinicians will be better able to optimize the design and delivery of therapies to improve motor function following stroke if we can better understand - on an individual-by-individual basis – specific impairments after stroke.

Changes in descending neural control can affect motor control after stroke

Middle cerebral artery (MCA) occlusion is the most common type of stroke, accounting for more than half of first strokes in the 1000-patient Lausanne Stroke Registry (Bogousslavsky et al. 1988). The MCA provides blood flow to most of the lateral hemispheres – including portions of premotor, primary motor, primary somatosensory, and prefrontal cortices. In addition, MCA supplies parts of the internal capsule, particularly the posterior limb which contains corticospinal and thalamocortical projections; as well as the globus pallidus, putamen and caudate (Lundy-Eckman 2007).

Suminski and colleagues implicated cerebello-thalamo-cortical networks during a task requiring feedback control of hand position in neurologically-intact participants (2007). They also found task-related activity in prefrontal cortex, premotor cortex, supplemental motor area, and parietal cortex during stabilization of the hand (Suminski et al. 2007). These circuits involve sensory feedback and processing and are consistent with the necessity of knowing where the body is in space in order to effectively plan and execute movement (Sober and Sabes 2003). MCA occlusion would likely damage parts of these networks leading to motor deficits. Thus, it is not surprising that persistent motor deficits are observed in approximately half of stroke survivors (Roger et al. 2012).

Intact neural control of movement in the upper extremity

A neurologically intact human can use the arm to make movements that are fast, smooth, and accurate. The corticospinal tract (CST) carries information for conscious control of fractionated movement in neurologically-intact humans. Primary motor cortex (M1) is the primary planning output center of the corticospinal tract. The majority of intracortical connections in M1 occur within a radius of 1 to 2 mm, suggesting that this proximity is functionally important (Scheiber 2001). M1 has a somatotopic organization that is highly consistent with observed functional task-groupings of muscles in skilled, highly fractionated (individuated) motor control, e.g., representations of the thumb and wrist – which necessarily must work together – are highly overlapped, while representations of disparate parts – such as the thumb and the foot – do not overlap (Scheiber 2001). Thus, M1 is organized in a manner to facilitate fractionated control of functional task-related muscles.

The connection patterns from descending CST neurons are consistent with the hallmarks of skilled motor behavior in the human upper extremity, such as fractionated movement driven by selective activation of small groups of task-related muscles (Buys et al. 1986). Neurons descending from CST to the spinal cord are known to make direct connections with alpha-motoneuron (αMN) pools (Fig. 2.1, thick blue lines). Connections from a given descending CS neuron tend to be focused on a small number of motoneuron pools that are highly linked functionally (Buys et al. 1986), and can – through connections with spinal interneurons – exert both excitatory and inhibitory actions at the αMN level (Lundberg and Voorhoeve 1962).

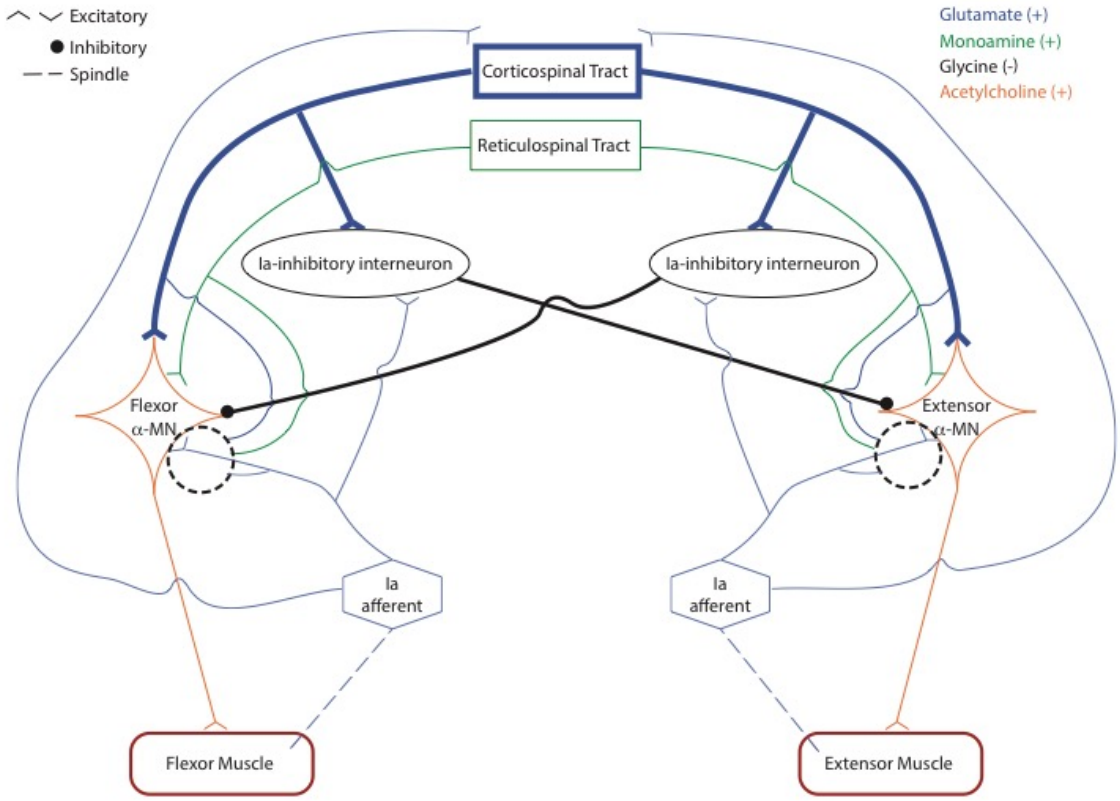

Figure 2.1: Descending control of volitional movement. Square boxes indicate motor tracts, concave diamonds indicate α-motoneruons, hexagons indicate Ia-afferents (dashed lines are muscle spindles), ellipses indicate Ia inhibitory interneurons. Dashed circles indicate location known to experience presynaptic inhibition, elaborated in next figure. Y endings indicate excitatory synapse, filled circle endings indicate inhibitory synapse. Blue traces represent glutamatergic (+) synapses, green traces indicate monoaminergic (+) synapses, orange traces indicate acetylcholinergic (+) synapses, and black traces represent glycinergic (-) synapses.

In addition to direct connections between CST and αMN pools, neurons from the CST also synapse with interneurons. The implications of these connections will be discussed further below.

Reticulospinal tract is viable candidate for restoration of motor function after damage to corticospinal tract

After stroke, many survivors recover motor control to some extent, but the recovered function may differ significantly from motor control prior to the stroke. Some have argued for the role of cortical reorganization and ipsilateral CST projections in motor recovery (c.f. Jang 2009). However, CST reorganization does not necessarily result in measurable improvement in motor function (Nudo et al. 2001). Under normal conditions CST is thought to inhibit the reticulospinal system (RS) both in the brain and at the spinal level (Ortiz-Rosario et al. 2014). After damage to the CST by stroke, RS may become the primary driver of motor function in the upper extremity (Baker 2011).

Recent experiments in nonhuman primates implicate the reticulospinal (RS) system as the primary motor tract responsible for recovery of motor function after damage to the CS tract (Zaaimi et al. 2012). Using a non-human primate model, Zaaimi and colleagues (2012) made extensive unilateral lesions in descending CS input to the spinal cord, effectively destroying contralateral CS input to the more affected side while leaving intact descending ipsilateral CS input from the intact hemisphere of the CS. Six months after the lesions were made, Zaaimi and colleagues made intracellular recordings of motoneurons innervating hand and arm muscles while stimulating either ipsilateral (intact) CS, or ipsi-, and contralateral RS targets. Stimulation in the ipsilateral CS did not provoke significant response in recorded motoneurons in either the lesioned animals or in non-lesioned controls. However, post-lesion stimulation of both the ipsilateral and contralateral RS tract led to increased response in recorded motoneurons compared with intact control animals, especially in recorded flexor motoneurons (Zaaimi et al. 2012).

This suggests that the RS is a good candidate for driving functional motor recovery after stroke, but only motor recovery within synergy patterns as all descending pathways originating in the brainstem, including RST, innervate pools of neurons for flexion / extension, not individual muscles for fractionated movement.

Neural causes of weakness after stroke

One commonly observed motor impairment after stroke is weakness (Kamper et al. 2002, Trombly 1992, McCrea et al. 2003, Canning et al. 1999). This may be due in part to changes in neural drive. While RS has been found to descend approximately in parallel with CS, excitatory post-synaptic potentials in αMNs resulting from RS input have approximately 20% of the amplitude observed from comparable CS input (Riddle et al. 2009). In the upper extremity, RS input has been shown to innervate flexors more than extensors (Baker 2011), consistent with observed imbalances in flexor and extensor strength after stroke (Beer et al. 2007). Additionally, connections from descending RS neurons tend to be spread across a larger number of αMNs and muscles with less focused drive than observed in CS (Peterson et al. 1975, Matsuyama et al. 1997). Thus, weaker, imbalanced, more highly dispersed descending input driven by RS would be expected to produce less neural drive – and therefore less muscle contraction and less torque production – than observed with intact CS control.

Additionally, involuntary co-contraction of muscles may contribute to observed weakness. One mechanism for reducing antagonist activity during volitional movement is reciprocal inhibition through Ia pathways (Fig. 2.1, Crone 1993). Ia pathways are modulated by Ia afferent input (which is excited by stretching muscle) as well as by

descending control from CS (Hultborn and Udo 1972). When descending CS input is lost, there is less excitatory input to the Ia inhibitory interneurons, which leads to a decrease in inhibition at the antagonist αMN. Thus, antagonist αMNs may be closer to threshold, which can lead to greater activity in the antagonist muscle prior to and during movement. Torque measured at a joint is the net torque produced by all muscles contracting across the joint. Thus, if there is elevated antagonist muscle tone (i.e., antagonist muscles are contracting), the forces exerted by those muscles will reduce the net force about the joint and contribute to measured weakness.

Neural causes of slowness after stroke

Another common motor deficit after stroke is slowness of muscle recruitment (Chae et al. 2002), torque production (McCrea et al. 2003, Canning et al. 1999), and movements (Roby-Brami et al. 1997, Levin 1996, Cirstea and Levin 2000, Trombly 1992, Kamper et al. 2002). Potential neural contributors to slowness after stroke include differences in neurotransmitters between the CS and RS, weaker and less focused descending input from RS drive, and decreased CS drive of Ia inhibitory pathways acting on task-antagonist muscles.

While both CS and RS pathways are known to directly innervate αMNs (see Fig. 2.1), differences in the time course of activation may result from differences in neurotransmitters released by the two pathways. The primary neurotransmitter of CS is glutamate (Al Masri 2011) while monoamines such as serotonin and norepinephrine are more prevalent in RS (Lundy-Eckman 2007). Glutamate is a fast-acting excitatory neurotransmitter with synaptic action on sub-millisecond time scales between release and

inactivation (Danbolt 2001). Monoamines are slow-acting neurotransmitters with synaptic action ranging from 10 ms to multiple-minute time scales (Lundy-Eckman 2007). The slower excitation of αMNs by the monoaminergic RS may contribute to slower activation of muscle after stroke.

In addition to releasing slow-acting monoamines, connections between the RS and αMNs are both weaker and more diffuse than those made by the CS. While the implications of this with respect to torque production are discussed above, it is important to note that strong, concurrent ("bursting") innervation of functional task-related αMN pools is also crucial to driving the functional task-coordinated muscle activation underlying fast movement of a limb segment about a joint. For example, in order to perform a ballistic movement, such as throwing a ball, many task-related muscles must activate concurrently in a small time window to produce the power needed to launch the projectile (ball).

Additionally, for fast movements to occur, antagonist muscle activity must be suppressed to prevent "braking" of the movement. In the intact motor system, CS pathway facilitates the suppression of antagonist muscle activity through inhibitory Ia pathways (see Fig. 2.1). CS makes synapses directly onto Ia-inhibitory interneurons that project onto antagonist αMN pools while simultaneously projecting axon collaterals onto agonist αMN pools (Fig. 2.1; Lundberg and Voorhoeve 1962, Hultborn and Udo 1972, Day et al. 1983, Cavallari et al. 1984). Thus, as the system is preparing to move but prior to volitional movement, CS can bring functional task-related agonist αMN pools closer to threshold while suppressing activation in antagonist αMN pools. This pattern of reciprocal agonist activation and antagonist suppression can facilitate fast responses and

accelerations at the onset of volitional movements. With loss of descending CS input, the Ia pathway must wait for input from afferents associated with muscle spindles which will not occur until after movement has begun and a muscle is stretched. Thus, the antagonist αMN pools will not be actively suppressed prior to movement potentially leading to delays in movement initiation as well as slower movement at onset due to resistance from residual antagonist muscle activation.

Neural causes of non-smooth control after stroke

Loss of smoothness is a hallmark of arm movement after stroke (Cirstea and Levin 2000, Dipietro et al. 2009, Krebbs et al. 1999, McCrea et al. 2005, Rohrer et al. 2002, Rohrer et al. 2004). Normal movement results from a combination of descending signals and afferent sensory signals (cf. Nielsen 2004). In neurologically intact humans, short point-to-point arm movements typically consist of a single smooth movement characterized by a smooth, bell-shaped tangential velocity profile (Fishbach et al. 2006, Cirstea and Levin 2000). Very long-duration arm movements – such as tracking an unpredictable target over several minutes – consist of a series of submovements at intervals of 400 to 500 ms (Craik 1947). These submovements are characterized by the presence of multiple peaks in the tangential velocity trace caused by proprioceptive feedback signals used to correct for perceived position errors (Vince 1948, Keller et al. 1996, Schaefer et al. 2009, Xu-Wilson et al. 2011). This observation is consistent with constant accumulation of error information and periodic discrete corrections. When proprioceptive feedback is lost, such as in large-fiber sensory neuropathy, submovements are eliminated and endpoint accuracy is degraded (Gordon et al. 1995). Thus,

proprioceptive feedback contributes positively to position accuracy and periodically modulates smooth movement in the intact human motor system.

Excitatory proprioceptive feedback to αMNs is modulated by presynaptic inhibition (Fig. 2.2) which causes release of the inhibitory neurotransmitter GABA onto the sensory afferent nerve's axon (Rudomin and Schmidt 1999) and thus prevents neurotransmitter release by that nerve. When the excitatory output from the afferent is suppressed, there is less excitatory input to the αMN, and thus less innervation of the muscle. Presynaptic inhibition is thought to have central origin and is affected by input from both the CS and RS tracts (Rudomin and Schmidt 1999). Additionally, presynaptic inhibition is affected by multiple afferent and spinal-level inputs (Rudomin and Schmidt 1999, Quevedo 2009).

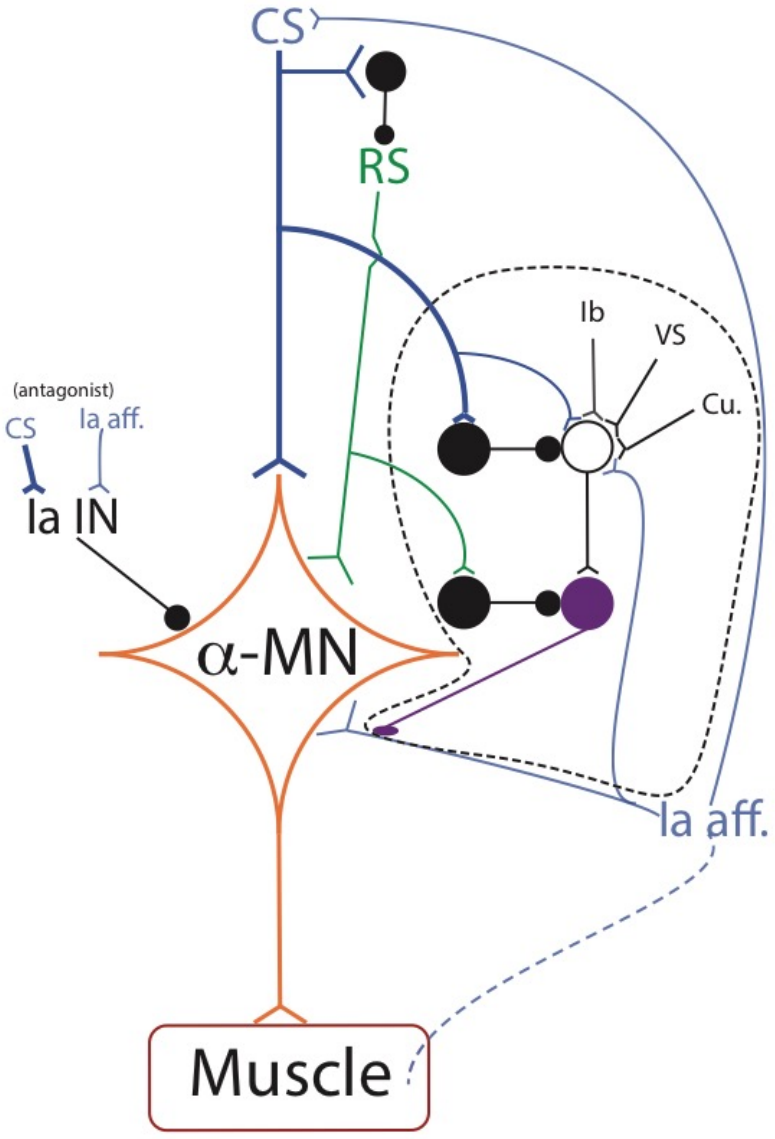

Figure 2.2: Descending and spinal inputs to α–motoneurons showing presynaptic inhibition. Y endings indicate excitatory synapse, ball endings indicate inhibitory synapse, ellipsoidal ending indicates GABAergic inhibitory synapse. Dashed shape encloses mechanisms of presynaptic inhibition including a 1st order primary afferent depolarization (PAD) interneuron, white circle with black excitatory axon, and last-order PAD interneuron, purple circle with inhibitory axon, and inhibitory interneurons, black circle with inhibitory axon. CS: Corticospinal tract, RS: reticulospinal tract; Ia cells in Ia reflex pathways including afferent (dashed line and blue excitatory axons and synapses) and inhibitory interneuron (black axon with ball end); Cu.: cutaneous afferent, VS: vestibulospinal system; Ib: Ib afferent. Blue traces represent glutamatergic (+) synapses, green traces indicate monoaminergic (+) synapses, orange traces indicate acetylcholinergic (+) synapses, purple oval traces represent GABAergic (-) inhibitory synapses, and black ball-ended traces represent glycinergic (-) synapses.

Presynaptic inhibition is a process involving a series of interneurons, the most significant of which are 1st order primary afferent depolarization (PAD) interneurons (Fig. 2.2, white excitatory interneuron) and last-order PAD interneurons (Fig. 2.2, purple inhibitory interneuron). 1st order PAD interneurons are excitatory interneurons that receive excitatory input from Ia, Ib, cutaneous, vestibuolospinal and CS sources, as well as indirect inhibition from CS (Rudomin and Schmidt 1999, Pierrot-Deseilligny and Burke 2005). When sufficiently excited, 1st order PAD interneurons excite last-order PAD interneurons to drive presynaptic inhibition, thus reducing excitatory afferent input to the αMN and indirectly decreasing the amount of excitation to muscle. In addition to excitatory input from 1st order PAD interneurons, last-order PAD interneurons also receive indirect inhibition from the RS pathway (Rudomin and Schmidt 1999, Pierrot-Deseilligny and Burke 2005). This connection allows RS drive to *suppress* presynaptic inhibition, thus allowing *more* excitatory afferent signal into the αMN. If the CS has suffered significant damage leaving the RS to modulate presynaptic inhibition, it is likely that presynaptic inhibition would be depressed and more afferent excitation would bombard αMNs.

Unregulated afferent input to αMNs extinguishes smooth movement. Fink and colleagues (2014) created a mouse model in which the last-order PAD interneurons were eliminated. The loss of these inhibitory GABA-ergic projections to sensory afferents – such as Ia proprioceptive afferents – greatly decreased regulation of excitatory signals from afferents to αMNs. This unregulated excitation precluded smooth movement in the forelimb of the mouse. Thus, appropriate regulation of proprioceptive feedback is essential to motor control and execution of smooth movements.

After stroke, there are several potential drivers of degraded proprioceptive integration that may contribute to jerkiness of movement. First, damage to sensory areas or connecting tracts within cortex could interfere with cortical perception of afferent signals and their integration into motor planning and execution. Second, if cortical regions involved in regulating presynaptic inhibition are damaged, direct afferent signals to αMNs may lack appropriate regulation. Finally, even if proprioceptive feedback is somehow unaffected by a stroke, slowness of movements could lead to more instances of the natural corrective interruption cycle that underlies submovements in the intact motor system – as seen in tracking tasks performed by neurologically-intact humans (Craik 1947).

Neural causes of elevated muscle activation and co-activation after stroke

The presence of persistent muscle activation after volitional movement is completed is widely observed in stroke (Burne et al. 2005, Chang et al. 2013, Mottram et al. 2009, 2010). In order to make a simple movement, such as flexing the elbow joint, the agonist muscles (in this case elbow flexors) must be activated while the antagonist muscles (in this case elbow extensors) are suppressed. If activity in the antagonist muscle is not effectively suppressed, the agonist muscle must contract more forcefully to overcome the antagonist contribution. In the intact motor system, the CS suppresses activity in task-antagonist muscles by inhibiting antagonist αMN pools.

When descending CS input to Ia inhibitory interneurons is lost, the ability to suppress activity in the task-antagonist αMN pool prior to movement onset is impaired because the Ia inhibitory interneurons target antagonist αMN pools (see Fig. 2.1).

Additionally, loss of descending CS input to 1st order PAD interneurons could decrease the amount of presynaptic inhibition acting on afferent terminals. This can lead to activation of the antagonist muscle during a functional task. During movement, the antagonist muscle is typically stretched, thus exciting Ia afferents which make excitatory monosynaptic connections with the antagonist αMN pool (see Fig. 2.1). Presynaptic inhibition is an effective mechanism for suppressing that excitatory monosynaptic stretch reflex (see Fig. 2.2). Thus, decreased presynaptic inhibition can contribute to greater activation of antagonist muscles during movement, and therefore can lead to greater co-activation.

Additionally, the slower time course of monoaminergic excitatory input from the RS system can lead to long-duration muscle activation compared with the fast-acting glutamatergic excitatory input from CS. While glutamate can be inactivated on a sub-millisecond time course, monoamine neurotransmitters can persist for tens to tens-of-thousands of milliseconds (Lundy-Eckman 2007). This persistent, monoaminergic excitation of αMN pools by descending RS input can lead to elevated co-activation in many functional tasks that require reciprocal activation of agonist / antagonist muscle groups. In a task such as cutting food with a knife – neglecting activation at hand, wrist and shoulder – elbow flexors and extensors can alternate their roles as agonist and antagonist on sub-second time scales. If there is long-acting excitation on either muscle group that is not effectively suppressed by functional inhibition, it stands to reason that one would observe elevated levels of co-activation during such a task.

Stroke related changes in muscle

Stroke-related changes in descending control can lead to changes in muscle composition. These compositional changes can lead to alterations in muscle properties that can have functional impacts on strength, speed, and smoothness.

Motor units and muscle fiber types

There are three predominant types of motor unit in humans: slow units, fast fatigue-resistant units, and fast fatigable units. These motor units are highly associated with the three most common muscle fiber types found in humans (Lieber 2002). Slow motor units are typically associated with slow oxidative (type I) muscle fibers which develop tension at the slowest rate and tend to create the smallest amount of tension amongst the fiber types. Slow oxidative muscle fibers also are the most fatigue-resistant type. Fast fatigue-resistant motor units are typically associated with fast oxidative-glycolytic muscle fibers (type IIa). These muscle fibers create force more quickly and typically create more tension than slow oxidative muscle fibers, but they also fatigue more quickly. Fast fatigable motor units are typically associated with fast fatigable muscle fibers (type IIb). Of the common muscle fiber types, these usually develop the largest tension, contract the fastest, and fatigue the fastest.

After stroke, the proportion of muscle fiber types may change within muscle. In the more impacted vastus lateralis (DeDeyne et al. 2004) and rectus femoris (Severinsen et al. 2016), muscle fiber composition was observed to skew to a greater percentage of fast fibers after stroke compared with the less impacted side. In the contralesional tibialis anterior, however, muscle fiber composition changed to have a greater percentage of slow

muscle fibers compared with the ipsilesional muscle and with muscle biopsies from neurologically intact controls (Frontera et al. 1997). Interestingly, the clinical significance of muscle fiber changes on decreased force production after stroke may be small. Severinsen and colleagues (2016) found that isometric force production in the more impacted rectus femoris of 36 stroke survivors in the chronic phase of recovery was not correlated with proportions of muscle fiber types, but was correlated with mean muscle fiber cross-sectional area.

Muscle mechanics affect force production and velocity

Individual muscle fibers have an optimal length at which the contractile elements are optimally overlapped and can create maximal isometric force. When the muscle fiber is lengthened, force decreases due to lack of overlap in contractile elements, and when the muscle fiber is shortened, force decreases due to excessive overlap of contractile elements (Lieber 2002). This length-tension relationship appears to be reflected in whole muscle activation, i.e., the maximal isometric torque a muscle can produce is dependent on the joint angle at which it held. When the joint is at its optimal angle, the maximal possible volitional torque is at its highest level (cf. Rack and Westbury 1969).

In some survivors of stroke, individual muscle fibers shorten, which can reduce the maximal force produced by individual muscle (Gray et al. 2012). Additionally, total maximal force production for whole muscles in the more impacted limbs tends to decrease. Survivors of stroke frequently have severely compromised force production when the muscle is shortened which can further reduce functional range of motion (Gray et al. 2012). One potential reason for this would be that when a muscle is greatly

shortened, its opposing antagonist muscle is generally lengthened. If the lengthened muscle is producing force (passively or actively, see below for further discussion), the shortened agonist muscle may not be able to generate enough force to create a net joint torque. Often, the joint angle at which optimal torque can be produced after stroke no longer coincides with functional behaviors.

Additionally, the amount of force a muscle can produce is dependent on the velocity of contraction and whether the muscle is shortening or lengthening during contraction (Lieber 2002). When a muscle is actively shortening, it cannot produce more force than it would isometrically. As velocity of muscle shortening increases, the maximum force that the muscle can produce decreases precipitously. When an active muscle fiber is lengthened, however, it can produce *greater* forces than are observed isometrically due to increased resistance from the stretching of elastic connective tissues. The force-velocity relationship is most studied in the shortening (concentric) case. In this case, as velocity of muscle contraction increases, the maximal force the muscle can generate decreases. Similarly, as load increases, the rate at which a shortening muscle contracts must decrease. After stroke, the greatest deficits of force production are observed in concentric contractions, with smaller deficits in isometric force production, and the smallest deficits in eccentric contractions (c.f. Gray et al. 2012). Additionally, survivors of stroke may not be able to achieve high volitional movement velocities (Gray et al. 2012).

Muscle architecture affects contraction velocity and force production

The maximal physiological limit of muscle contraction is determined by muscle fiber length. Fiber length determines the possible change in length of the muscle fiber and the maximal velocity at which it can contract. Longer fibers are able to contract more quickly than shorter fibers and can cover a greater distance as they shorten (Lieber 2002). After stroke, decreases in muscle fiber length have been observed in the more impacted gastrocnemius and brachialis (Gray et al. 2012). These changes in muscle fiber length, and the concomitant shortening of muscle frequently observed after stroke, would lead to decreases in maximal muscle contraction velocity (due to reduced contraction velocity of shorter fibers) and to reduced range of motion.

Force production of muscle is related to physiological cross-sectional area (PCSA). PCSA is a value calculated to model the theoretical cross-sectional area of all muscle fibers within a given muscle. PCSA is determined by the equation:

$$PCSA = \frac{m * \cos(\theta)}{\rho * l_{fiber}} \qquad \text{[Eq. 2.1]}$$

where m is the mass of the whole muscle, θ is the pennation angle of the muscle fibers, ρ is a constant value denoting the density of muscle, and l_{fiber} is the muscle fiber length (Lieber 2002). Thus, a muscle's PCSA increases as muscle mass increases, as pennation angle decreases with respect to the axis of force production, or as fiber length decreases.

While muscle fibers have been observed to shorten after stroke, and the few studies on pennation angle of muscle after stroke show that it tends to decrease relative to the axis of force production, weakness is still among the most commonly described physical deficits after stroke (Gray et al. 2012). Given that these observed changes in fiber length and pennation angle would serve to increase PCSA, this suggests that

reductions in muscle mass are the predominant driver of lost PCSA-related force production capacity after stroke.

In addition to PCSA, force production of muscle is also related to the maximal stress capacity of the muscle (Zajac and Winters 1990). Maximal stress capacity is the largest amount of force per unit of cross-sectional area that the muscle can generate. Maximal stress is related to the quality and alignment of contractile fibers (JM Winters, Personal Correspondence, November 2017) as well as resting sarcomere length (Taylor 2000). Taylor found that as resting sarcomere length increases, the maximal stress capacity of muscle – and therefore the maximal force production of otherwise similar muscles – increases (2000). After stroke, muscle fibers have been observed to shorten (Gray et al. 2012) which would contribute to decreased maximal stress capacity and thus to decreased force production capacity.

Imaging studies have found decreases in anatomical cross-sectional area of muscle in the more impacted upper arm, forearm, and thigh after stroke (Berenpas et al. 2016, Hunnicut and Gregory 2017, Ryan et al. 2002). A systematic review found that decreases in lean muscle mass on the more impacted side range from 4.5% to 14.5%, compared with the less impacted side (English et al. 2010). These decreases are likely related to a decrease in the quantity of contractile fibers on the more impacted side. Hafer-Macko and colleagues (2008) performed a Western blot analysis comparing the quantity of myosin heavy chains in the more impacted and less impacted vastus lateralis. They found decreases in the quantity of myosin heavy chains associated with every muscle fiber type in the more impacted muscle than in the less impacted muscle. This result suggests that there is a decrease in the number of contractile fibers in the more

impacted muscle, therefore it would not be surprising that there is a loss of force capacity. This loss of lean mass directly contributes to decreased PCSA. Overall, decreases in lean mass and anatomical cross-sectional area of muscle (partially due to decreases in the amount of myosin heavy chains) indicate that architectural changes in contractile tissue degrade force production capacity after stroke.

Furthermore, there are changes in non-contractile elements of muscle after stroke that may have functional importance. Infiltration of intramuscular fatty tissue has been recorded in the more impacted thigh of chronic-stage stroke survivors (Hafer-Macko et al. 2008, Ryan et al. 2002). Additionally, spastic muscles have been observed to have greater collagen accumulation and demonstrate greater stiffness than comparable muscles from neurologically intact controls (Booth et al. 2001, Eby et al. 2016, Friden and Lieber 2003). These phenomena suggest changes in structural components of the muscle (such as collagen and titin; Lieber 2002) and would likely cause increases in the force exerted when passively stretching muscle. For example, if the passive force created by the stretching triceps increases as the biceps concentrically activate to flex the elbow, the biceps would need to create greater force to overcome the passive force of the triceps muscle and achieve the same net torque about the elbow.

Finally, tendon properties may also change after stroke. The Achilles tendon in the more impacted leg has been found to lengthen and become more compliant (Gray et al. 2012). Changes such as these would make tendon less capable of quickly and effectively transmitting forces from a contracting muscle to the skeleton. Thus, after stroke, muscle function may be further impaired by infiltration of fatty tissue, changes in

structural proteins such as collagen and titin that alter the passive properties of the muscle, and reduced capability of tendons to effectively transmit force.

Post-stroke motor impairments are also due to changes in descending control and muscle remodeling

Weakness after stroke has both neural and muscular causes. Potential neural contributors include decreased and more diffuse descending drive to motor units which would decrease agonist force production, as well as decreased inhibition in task-antagonist muscles prior to and during movement, which would increase antagonist tension against the intended movement. Potential muscular contributions include loss of lean muscle mass, degraded quality of myo-tissue, and decreases in PCSA (and therefore force generation capacity) as well as increased passive tension in muscles which would increase opposing force.

Slowness observed after stroke also likely has both neural and muscular causes. Potential neural contributions include decreases in descending control of Ia pathways (see Fig. 2.1) which can, in intact motor control, perform early recruitment of task-agonist motor units while inhibiting activity in task-antagonist motor units prior to the start of movement allowing for fast launch of movement. Impairments in this mechanism after stroke could result in slower launch of movement. Additionally, simple loss of quantity or quality of descending drive may reduce the ability to concurrently activate a large number of motor units. Potential muscular contributions to slowness include the force/velocity characteristics observed after stroke due to decreases in PCSA and muscle fiber length. The force capacity of muscle fibers, and whole muscles, tends to be reduced after stroke. Force production during concentric contractions is most degraded by stroke.

This is disadvantageous for creating fast movements, especially those that must overcome resistance from pathological stiffness (passive or active) in lengthening task-antagonist muscles. If overall force capacity is decreased, and lower velocity movements are capable of creating greater forces than higher velocity movements, slowness could be used as a compensatory behavior.

Loss of movement smoothness is another characteristic frequently observed after stroke. Long-duration movements tend to involve proprioception-driven submovements (which increase measured jerk). Improper descending modulation of proprioceptive signals into activity at the motor units can interfere with the production of smooth movement. Further, the degradation of sensory integration with movement at a central level could impair planning of smooth movement. Additionally, changes in distribution of muscle fiber types, combined with changes in descending innervation, could interfere with smooth or sustained recruitment of muscle fibers leading to jerky movement. Finally, increased stiffness combined with weakness could lead to slower, longer duration movements that allow more time for proprioceptive corrections to take place.

It is difficult to disambiguate between the neural and muscular causes of motor impairment after stroke

It is difficult to clinically – or experimentally – tease apart stroke-related neural and muscular contributions to motor dysfunction. After stroke, there are bilateral changes in muscle architecture that are not explained by a simple disuse model, suggesting that there may be a neural component to muscle remodeling (Berenpas et al. 2017). Thus, even the physical manifestation of muscle – which contributes largely to its function – is highly interlinked with neural deficits.

Additionally, within stroke, there can be differing etiologies for apparently similar motor dysfunction. For example, in a study by Eby and colleagues (2016), all stroke survivors tested demonstrated increased passive torque production in the more impacted arm compared with the less impacted arm. However, muscle biopsies showed increased shear modulus (muscle stiffness) in only half of the participants, but not in the other half. Thus, the same observable phenomenon (passive torque generation) had clearly differing causes within the group of similarly-presenting participants. These differences would not have been distinguishable without the use of invasive and labor-intensive methodologies.

Coordination of multiple muscles

If one considers a simple, two-muscle model consisting of a task-agonist and a task-antagonist that move a joint, the difficulty of separating neural and muscular contributions becomes clear. To perform fast, controlled targeted movements, agonist and antagonist muscles must work together coordinating activation timing and magnitude, force production and velocity. In a neurologically intact motor system, the agonist muscle produces a burst of activity (muscle activation) at the beginning of movement, becomes close to quiescent during the middle, and then is activated again toward the end of movement. The antagonist is active at a time that largely overlaps the quiescent period in the agonist. This pattern of activation allows for a fast launch of movement, followed by quick movement cessation, and damping at the end of movement to prevent oscillation about the endpoint (c.f. Marconi et al. 2006).

Execution of this series of events requires exquisite descending control activating the correct motor units at the correct time, fast response from the motor units, fast

activation of muscle, and quick deactivation of muscle as well. This combination would allow the agonist to create an appropriate level of force quickly, and allow the antagonist to remain largely inactive except to help stop the movement and stabilize the limb when required. As described above, the ability to quickly create force in the agonist can be impaired both by loss of descending drive and changes in muscle properties. Likewise, increases in antagonist force production can be either neural or muscular in origin. These neural and muscular contributors intertwine to create the weakness, slowness, and jerkiness of movement so often observed after stroke.

Rehabilitation of upper extremity motor function after stroke

The four most common impairments in the upper extremity after stroke are loss of fractionated movement, abnormalities in muscle tone, somatosensory impairments, and paresis (Lang et al. 2013). Fractionated movement refers to the ability to activate single muscles, or very small functional groups of muscles, in isolation of other muscle in order to move selective joint segments. Abnormalities in muscle tone can refer to either hypotonia, in which there is a lack of muscle tone, or hypertonia, in which there is excessive muscle tone. Somatosensory impairments can include lost or impaired light touch, kinesthesia (motion sense), or position sense. Paresis, the decreased ability to activate motor units and therefore decreased ability to activate muscle, accounts for the majority of lost upper extremity function after stroke (Lang et al. 2013, Winstein et al. 2016).

While much of motor recovery after stroke is spontaneous, there is evidence that natural recovery alone does not account for all improvement in disability observed after

stroke (Teasell et al. 2003). Rehabilitation has been shown to improve motor function (Hebert et al. 2016, Stroke Foundation 2017, Winstein et al. 2016). Additionally, rehabilitation can improve quality-of-life outcomes after stroke, such as increasing the likelihood of being discharged to home rather than remaining institutionalized for life, enhancing recovery, and increasing independence in performing activities of daily living (Winstein et al. 2016).

Measures of rehabilitation: Function and impairment

In stroke rehabilitation, "function" generally refers to the ability to perform a task, such as buttoning a shirt or pouring a glass of water. The term "impairment" generally refers to limitation in body structure or function, such as decreased pinch-grip strength or wrist extension. Function and impairment are related, but it is not a one-to-one negative correlation. Improvements in function can be achieved without any change to impairment by modifying movement patterns to achieve a task-goal (e.g., leaning with the trunk to compensate for decreased elbow extension, stabilizing an object against a surface to compensate for weakness, or using the less-affected hand to perform a task). These modifications are also called compensatory movements. Impairment, however, cannot be addressed through compensation.

Impairment-focused training

Resistance training after stroke can increase muscle cross-sectional area, decrease intramuscular fat, and decrease myostatin – a substance which inhibits growth of muscle tissue (Ryan et al. 2011). However, there is strong evidence that while strength-training

therapies can be beneficial for general health after stroke, they are ineffective for improving function in the more impacted upper extremity (Eng 2004, Teasell et al. 2003). This may be due to the fact that many functional tasks require dexterous use of the hand, which is not addressed by resistance training.

Task-oriented training

Task-oriented rehabilitation involves training survivors of stroke on tasks that replicate or relate to the types of behaviors that are used to perform daily activities. There are two primary approaches to task-oriented rehabilitation: Restorative and compensatory (Lang et al. 2013). In restorative therapy, the primary focus is on reestablishing motor patterns to an "intact" state. This approach may be more appropriate for patients with mild impairment. Patients with mild impairment may have more residual corticospinal input, and could – perhaps – use plasticity in the corticospinal tract to re-learn skilled behaviors. The corticospinal tract is responsible for the fractionated motor control characteristic of much of functional use of the hand and arm (Buys et al. 1986, Scheiber 2001).

In compensatory therapy, the goal is to maximize function, i.e., to help the patient achieve the functional objective by whatever means necessary including using one hand or through the use of adaptive tools (Lang et al. 2013). Compensatory therapy may be a more appropriate approach for those with greater impairment who are unlikely to ever substantially recover lost control of the hand and arm. For patients with more severe injuries to the corticospinal tract, there is no known neural system that can replace the fractionated movement required for full use of the hand, and thus there is no secondary

neural system thought to be capable of fully "restoring" motor patterns making compensation a viable alternative.

There is strong evidence that task-oriented training improves functional recovery (i.e., ability to perform specific tasks), although it may not reduce impairment (such as pinch grip strength). This suggests that much of functional recovery may be more compensatory (achieving the end goal regardless of method used) rather than restorative (performing a task in the same manner as one who has not had a stroke) (Quinn et al. 2008, Langhorne et al. 2011).

Only a small subset of patients, i.e., those whose CS tract is largely intact, are capable of regaining "normal" motor function. Thus, while restorative therapy is obviously appropriate for patients with very mild impairment, and compensatory therapy is appropriate for those with severe impairments, it is more difficult to predict in patients with moderate impairments if restorative therapies will be effective, or if the patients would be better served by compensatory therapy. Advances in testing methodologies for the intactness of the CS tract may help rehabilitation professionals set appropriate goals and select appropriate rehabilitation methodologies to achieve the best possible outcomes.

Factors that improve rehabilitation outcomes

Post-lesion neural plasticity begins within a few hours of stroke onset (Oujamaa et al. 2009). Thus, the current best-practice for stroke treatment is that patients are admitted to interdisciplinary stroke rehabilitation units as soon as they are medically stabilized (Teasell et al. 2003, Quinn et al. 2008). Interdisciplinary stroke rehabilitation teams

consist of a clinical social worker, psychologist, physiatrist, rehabilitation nurses, and physical, occupational and speech therapists depending on the patient's needs (Bukowski et al. 1986). Treatment in the specialized stroke unit includes any standard medical care necessary, combined with early exposure to formal restorative interventions administered by the therapy team, as well as more frequent and consistent encouragement to use the more impacted arm outside of formal therapy such as a rehabilitation nurse requiring a patient to reach and grasp a cup of water rather than bringing it to the patient's mouth directly. Additionally, members of the interdisciplinary team coordinate their efforts to make sure the patient is receiving the best care available as he or she progresses through recovery.

There is strong evidence associating early mobilization, which is more likely to happen within a specialized stroke unit than in a standard medical ward, with improved outcomes after stroke (Teasell et al. 2009). Care given in a specialized stroke unit has been demonstrated to provide long-lasting functional gains (Hebert et al. 2016, Stroke Foundation 2017, Teasell et al. 2003, Winstein et al. 2016). Additionally, this approach has improved quality-of-life outcomes including reduced mortality, decreased dependency, decreased length of hospital stay, and increased likelihood of discharge to home compared with treatment on a standard medical ward (Hebert et al. 2016, Teasell et al. 2009). Current recommendations for stroke rehabilitation include mobilizing the patient within 24-48 hours of stroke once he or she has been medically stabilized. Patients who have enough rehab needs and the ability to tolerate 3 hours of therapy a day are then recommended to go to Inpatient Rehabilitation for a minimum of three hours of task-specific therapy per day delivered by an interdisciplinary stroke team. Upper

extremity treatments are patient-specific depending on his or her specific deficits and goals (Hebert et al. 2016, Stroke Foundation 2017, Winstein et al. 2016).

Multiple randomized controlled trials have provided strong evidence that greater intensity of therapy results in improved function after stroke (Han et al. 2012, Quinn et al. 2008, Teasell et al. 2003), although increased intensity of therapy may not improve measures of function that rely heavily on hand function (Winstein et al. 2016). In a review of randomized controlled trials, Oujamaa and colleagues (2009) found evidence that increasing early stroke rehabilitation (during the second through fifth weeks after stroke onset) from 10 hours to 25 hours over four weeks was associated with significant, long-term improvements in hand function. Similar correlations between intensity (in hours) of outpatient rehabilitation and degree of improvement have been reported (Dombovy et al. 1986). In chronic stroke, moderate increases of classic rehabilitation therapy in an outpatient setting (9 hours) were not found to lead to improvements, but large doses (57 hours) led to functional improvement in moderately impaired individuals (Oujamaa et al. 2009). Han and colleagues (2012) observed significant improvements in impairment scores in survivors of stroke in the acute phase of recovery: patients receiving 3 hours of therapy per day had significantly greater improvements in two measures of upper extremity impairment compared with patients who had received one hour of identical therapy.

Effective therapy for the upper extremity and promising experimental results

Constraint Induced Movement Therapy (CIMT) is a rehabilitation protocol which combines intensive therapy doses with forced use of the more-affected arm and hand

during activities of daily living outside of rehabilitation (Taub et al. 2006). Over the course of CIMT, patients are given 6 hours of training by a physical therapist each day for 10 days over the course of 2-weeks. The therapy portion of CIMT consists of restorative "shaping" of motor patterns. In this protocol, tasks are selected that address the individual patient's motor deficits, then ideal task performance is modeled by the therapist, the patient is prompted/cued to perform the task in the ideal manner, and is given immediate feedback on speed and quality of movement. Difficulty of the tasks increases as the patient proceeds through therapy. In addition to 60 hours of formal therapy, the less-impacted arm is immobilized for 90% of the patient's waking hours throughout the therapy window to encourage use of the more impacted arm and hand in activities of daily living. CIMT has been demonstrated to lead to significant improvement in functional ability of the upper extremity after stroke (Taub et al. 2006) and is the most effective protocol currently available for upper extremity rehabilitation (Oujamaa et al. 2009). CIMT is, however, limited to those individuals who have some active wrist and finger extension to begin with, as the original animal model of forced use was based on a deafferented animal model with intact descending corticospinal pathways but absent afferent sensory feedback (Taub 1993).

The intensive, individualized training that is a hallmark of CIMT makes it very costly to administer, given the large number of therapist hours required (Wolf 2007). It is also very frustrating for participants with a significant drop out rate (Wolf, personal conversation). There is some evidence that another upper extremity rehabilitation protocol, the Bobath Concept, may be able to deliver similar functional gains in mildly-impaired survivors of stroke with fewer therapist hours required (Huseyinsinoglu et al.

2012). Additionally, while early studies of CIMT showed significant improvements on research measures, it is not clear that these improvements are clinically significant (Wolf 2007), and the impacts of CIMT may not be long-term. A Cochrane Review of the studies of CIMT found that most studies concluded there was no persistent benefit of having received CIMT 6 months after the end of therapy (Sirtori et al. 2009). Finally, the applicability of CIMT to the majority of survivors of stroke is limited. Participants in the randomized controlled trials testing CIMT were limited to those who could voluntarily produce ≥ 10° of extension at the metacarpophalangeal and interphalangeal joints, and ≥ 20° of extension at the wrist (Taub et al. 2006). This capability is characteristic of relatively mild impairment, and may suggest that the corticospinal tract is at least partially intact in these individuals (Winstein et al. 2016, cf. Zaaimi et al. 2012). Unfortunately, this level of impairment describes a minority of hemiplegic stroke survivors, estimated to between 5 and 30% of stroke survivors (Wolf 2007).

Robotic therapy for the upper extremity allows for increased dosage with less hands-on time from a therapy professional, and thus can decrease treatment cost of high-dose rehabilitation therapy. Most robotic approaches allow the patient to perform repetitive tasks involving repeated movement of the shoulder, elbow, and in some cases the wrist (Oujamaa et al. 2009). Patients receiving robotic therapy for the upper extremity generally show improved use of the joints trained but these improvements do not transfer to significant improvements in use of the hand which is not trained (Teasell et al. 2009). Thus, while robotic therapy may potentially reduce specific impairments after stroke, it does not necessarily contribute to improvements in function (Kwakkel et al. 2008, Oujamaa et al. 2009). For example, improved strength and range of motion of

the elbow may reduce impairment in reaching, but without improvement in hand function, ability to perform functional tasks with the more-impacted arm will still be limited.

Additionally, recent research has produced several promising techniques and tools that may improve rehabilitation outcomes. Visualization of motor activities, when used in combination with physical rehabilitation, has been found to improve both motor impairment and arm function in those with moderate impairments and no cognitive deficits (Ojuamaa et al. 2009). Electrical stimulation of distal portions of the median, ulnar, and radial nerves of the more affected arm in conjunction with physical rehabilitation was shown to improve paretic hand function in chronic stoke patients, though the result was not long-lasting (Oujamaa et al. 2009). Finally, Lang and colleagues (2013) recommend the use of accelerometry for tracking the effectiveness of therapeutic interventions in increasing use of the more-impacted limb. Here they placed an accelerometer on each of the stroke survivor's wrists, and used the data as a method for quantifying the impact of therapeutic interventions on actual daily use of the more impacted arm after stroke so that therapeutic approaches may be evaluated and changed in light of empirical outcomes.

Limitations to upper extremity motor rehabilitation after stroke

While rehabilitation does appear to contribute to improved quality-of-life outcomes after stroke, such as reduced mortality and increased likelihood of being released to home, its overall beneficial effects on motor control are modest (Teasell et al. 2003). In spite of hundreds of clinical trials of rehabilitation interventions, the extent of

damage to corticospinal pathways and the structural integrity of descending white matter pathways dictate the extent of possible upper extremity motor recovery (Stinear et al. 2012).

The best guideline for predicting upper extremity recovery is the PREP algorithm (Stinear et al. 2012). In this algorithm, patients are first tested 72 hours after stroke; patients who demonstrate shoulder abduction and finger abduction (i.e., have a manual muscle testing (MMT) score of 8-10/10 for those joints, which is indicative of relatively intact contralateral corticospinal control, cf. Zaaimi et al. 2012) are predicted to have clinically complete upper extremity recovery and can be discharged home with a home exercise program. Patients who score <8/10 often go to inpatient rehab, and can be tested at 2 weeks using transcranial magnetic stimulation to attempt to evoke motor potentials from the ipsilateral motor cortex; those who respond to stimulation have the potential for notable motor recovery. Patients who do not show either of these indications of some level of intact descending corticospinal control can undergo further testing in MRI to examine structural integrity of the descending white matter pathways; those with a low ratio of CS tract density between the two hemispheres have limited potential for upper extremity recovery, while those with a high ratio have no potential for upper extremity recovery.

The group who sees the greatest benefit (better quality-of-life outcomes, motor improvements) when receiving specialized rehabilitation care instead of purely medical treatment are those who have moderate rather than severe impairments (Teasell et al. 2009). Those with mild impairments may have enough residual function in the more impacted arm to begin spontaneously using it in daily life (and thus largely self-

rehabilitate). Those with severe impairments may lack the descending neural control to ever allow sufficient motor recovery of the more impacted limb for it to be used in daily life regardless of intervention. Thus, those with moderate impairment may not be able to fully restore motor control, but specialized training – restoring motor capability where possible and teaching compensation where necessary – may help them to achieve greater return of function than they would without intensive therapy.

However, even within the group of stroke survivors for whom rehabilitation would appear to be most useful, there can be variability in underlying factors contributing to clinically-identical symptoms (cf. Eby et al. 2016) as well as large differences in neural plasticity from person to person (Oujamaa et al. 2009). These differences can be difficult or impossible to distinguish through standard clinical observation (e.g., involved research methods, such as muscle biopsies or longitudinal studies of neural activity, are not part of clinical care after stroke). This variability makes designing, studying, and implementing effective interventions extremely difficult. Until we better understand the mechanisms underlying deficits after stroke, we do not have the tools to rationally and systematically develop better interventions.

Measurement of impairment and function after stroke

Given that stroke has highly variable impacts from one person to the next, it is important to quantify the deficits within each individual. This practice is useful in the clinic for selecting appropriate therapy and tracking progress. It is important in research because variations in motor performance during an experiment may potentially be explained by type or extent of deficits.

Composite measures of upper extremity impairment and function

The Fugl-Meyer Assessment of Sensorimotor Function (FMA, Fugl-Meyer et al. 1972) is a comprehensive impairment-based assessment of physical status and performance following stroke, which is measured by a Likert-type scale with a total of 266 points possible. The motor portions of these measures are defined by Brunnstrom's stages of recovery, beginning with complete flaccidity, progressing through the development of spasticity, synergistic movement, out-of-synergy movement, individuated joint control, and finally normal motor function (Sawner and LaVigne 1992). A subset of this section is the upper extremity motor evaluation (FM_M), which includes assessment of the Brunnstrom stages, including wrist and hand function, and tremor and dysmetria of rapid arm movements. The FMA is a gold standard clinical evaluation that has excellent intra- and interrater reliability for the measure in each subsection and as a whole (Gladstone et al. 2002). The FM_M can, however, be limited by ceiling effects. The use of a complimentary measure of function can provide additional information to better characterize meaningful motor deficits after stroke (Gladstone et al. 2002).

The Chedoke Arm and Hand Activity Inventory (CAHAI) is a clinical evaluation of bilateral upper extremity function after stroke that consists of 13 real-life tasks. These tasks reflect a full range of normative movements, pinches and grasps, and stages of motor recovery after stroke (Barreca et al. 2004, Sawner and LaVigne 1992). Examples of tasks include dialing a phone, opening a jar, and buttoning a shirt. Performance on each task is scored on a scale of 1 to 7. A score of 7 indicates complete independence, i.e., the participant was able to perform the task quickly and effectively without needing to stabilize the arm or objects. A score of 1 was awarded if the participant performed less

than 25% of the effort required to complete the task or if the task was deemed unsafe to attempt. This measure has high interrater reliability and is more sensitive to change in clinically important changes in arm impairment than the Action Research Arm Test, a comparable measure (Barreca et al. 2005).

Individual impairment measures

The upper extremity FMA includes a sensory subsection that contains coarse measures of proprioceptive acuity (FM_P) and light touch (FM_{LT}; Fugl-Meyer et al. 1975). The test used in the FM_P is also known as the "up or down?" test. In this measure, the participant sits with the limb relaxed and eyes closed while the clinician supports the limb and moves a single joint up and down through a comfortable range of motion. When the clinician stops moving the joint, the participant is to report if the segment is extended, "up", or flexed, "down" (DeGowin et al., 1987; Epstein et al., 2008). The task is repeated six times at each the thumb, wrist, elbow, and shoulder. Proprioception at each joint is rated with a score of absent (0), impaired (1), or intact (2). In the light touch portion of the FMA (FM_{LT}), a clinician lightly touches the patient's more affected arm and hand. Sensation of light touch scored as absent (0), impaired (1), or intact (2) compared to the less affected limb. Interrater reliability of the sensory portion of the FMA is excellent in total. However, there are observed ceiling effects of the FM_P, and interrater reliability of FM_{LT} alone is moderate (Lin et al 2004).

The Arm Movement Detection Test (AMDT) is a robotic test of proprioceptive acuity in the arm that allows for fine discrimination in measurements of kinesthetic detection threshold. This research measure uses a horizontal planar robot to perturb the

hand. Participants complete 10 trials, alternating between ascending perturbations (0 to 2 N) and descending perturbations (2 to 0 N). As each trial progresses, the researcher asks "do you feel your hand moving?" The participant responds with "yes" or "no." The researcher then adjusts the amount of perturbation up or down to find the threshold of movement detection. The advantage of this measure is that it provides a ratiometric measure of one aspect of proprioception (kinesthesia), that can be compared to a normative range. The AMDT was found to reliably discriminate between those with intact and impaired proprioception and is reliable across repetitions (Mrotek et al. 2017).

The Modified Ashworth Scale (Ashworth 1964, Bohannon and Smith 1987) is a measure of muscle tone/spasticity determined by assessing velocity-dependent resistance to passive motion. A clinician supports the joint to be tested and moves it slowly to establish its available passive range of motion. The clinician then moves the joint quickly through the range of motion in flexion and extension. The resistance felt is graded on scale of 0 to 4. A score of 0 indicates that there is no increase in tone compared to the less-affected side (and is considered "normal"), and a score of 4 indicates muscle tone so severe that it renders the tested joint rigid. The MAS has good interrater reliability at the elbow when performed by a trained clinician (Bohannon and Smith 1987, Pandyan et al. 1999).

The Montreal Cognitive Assessment (MoCA, Nasreddine et al. 2005) is designed to test visuospatial/executive function, naming, attention, language, abstraction, delayed recall, and orientation and is sensitive to mild cognitive impairment. Scores range from 0 to 30 with ≥26 considered normal. The MoCA has high test-retest reliability and internal consistency. It also has high sensitivity and specificity while detecting mild cognitive

impairment in those without speech deficits, however scores can be artificially lowered in participants with expressive aphasia. Cognitive deficits can interfere with rehabilitation protocols (Oujamaa et al. 2009) and could potentially interfere with performance on research tasks.

Changes in isometric torque production and muscle function after stroke

Isometric tasks are a useful experimental paradigm because they allow one to collect data on torque production and muscle activity while minimizing the impact of uncontrolled, non-experimental changes in muscle length, joint angle, and velocity. McCrea and colleagues (2003) investigated isometric torque production by asking hemiparetic survivors of stroke and neurologically intact controls to perform cued maximal elbow flexion and extension exertions. Participants were instructed to develop maximal torque as quickly as possible, sustain that torque for 3 seconds, and then reduce torque as quickly as possible. This study reports that, compared with the neurologically intact controls, the more affected arm of stroke survivors demonstrated marked weakness and took longer to both develop and reduce torque. A similar finding was reported by Canning and colleagues (Canning et al. 1999). Consistent with previously discussed changes in neural and muscular systems after stroke, the ability to quickly modulate torque is impaired in chronic stroke.

Changes in muscle activation in single joint, isometric tasks

To better understand the role of delays in muscle activation and deactivation in the more affected limb after stroke, Chae and colleagues (2002) fixed the wrist in a

neutral position and asked stroke survivors to develop wrist flexor or extensor torque as forcefully and quickly as possible, and then to relax the muscle as quickly as possible in response to an auditory cue. Electromyographic activity of primary wrist flexors and extensors was analyzed to estimate the time-delay between cue transitions and changes in EMG activity relative to baseline activity. The authors found that muscles in the more affected arm demonstrated significantly greater delay in initiation and termination of muscle contraction relative to the less affected arm. These delays correlated significantly with upper limb motor impairment (FM_M) and physical disability (quantified by the Arm Motor Ability Test, which assesses ability to perform activities of daily living).

More recently, Chang and colleagues performed an isometric torque production experiment that examined the relationship between spontaneous discharge of motor units and spasticity, weakness, and force variability. Stroke survivors and neurologically intact participants generated cued submaximal isometric elbow flexion torque while intramuscular EMG activity in biceps muscles was recorded (Chang et al. 2013). While some intermittent spontaneous discharges were observed in resting biceps muscles in both groups (consistent with prior observations of Mottram et al. 2009 and Mottram et al. 2010), sustained increases in the *rate* of spontaneous discharges were observed after voluntary activation only in the more involved limb after stroke (Chang et al. 2013).

Joint-position dependence of muscle function after stroke

Several research groups have found that properties of muscle activation can vary with limb position after stroke. Kamper and colleagues (2001) found that when taking a spasticity measurement in the more affected arms of chronic-stage stroke survivors, the

initial muscle fiber length had a significant impact on reflex response. As muscle fiber lengths increased (i.e., as the muscle lengthened/stretched) the magnitude of the reflex response increased. In addition, the reflex was triggered with less movement from the already stretched starting position compared to when the test was executed with the limb in a position that shortens the muscle. A related study of stroke survivors by Levin and colleagues (Levin et al. 2000) found that at the affected elbow, the static stretch reflex threshold for the biceps and triceps lay within the physiological range in 11/12 and 4/12 participants, respectively. This indicates that when the arm was physically between the static stretch reflex threshold and the physiological joint limit, Levin and colleagues observed involuntary muscle activation in recorded electromyograms consistent with hypertonia. This phenomenon was not observed in neurologically intact participants, as the static stretch reflex threshold for this group was consistently outside of the physiological range of motion.

Additionally, Levin and colleagues found that stroke survivors with abnormal stretch reflex thresholds showed reductions in maximal flexion and extension torques when the agonist muscle was in a shortened position. In some hemiparetic participants, joint-angle ranges were found in which no active torque could be produced either in extension, or in both flexion and extension while EMG recordings showed co-activation of the agonist/antagonist pair. The range in which reciprocally organized agonist and antagonist muscle activity could be generated was limited in all but one stroke survivor. These ranges were related to the boundary values of stretch reflex thresholds found during passive muscle stretch. Reductions in this range were correlated with motor impairment as quantified by the FM_M, suggesting that deficits of elbow torque production

and deficits of motor control are related. Unfortunately, no attempt was made to link these results to motor function, leaving unresolved the question of how joint angle-related deficits of motor control might contribute to deficits of motor function post-stroke.

Impairments of goal-directed arm movement after stroke

Reaching behaviors facilitate interaction with objects in the environment, which is essential for executing many functional activities such as brushing one's teeth. However, approximately half of stroke survivors must live with chronic motor deficits that impact many tasks including the simplest of point-to-point movements (Roger e al. 2012). These deficits can include limitations in range of motion, muscle weakness, slowness, segmented reaching, and inaccuracy in final hand position (Roby-Brami et al. 1997, Levin 1996, Cirstea and Levin 2000, Trombly 1992, Kamper et al. 2002).

Simple point-to-point movements consist of multiple control actions

A single point-to-point movement can be considered to be a 'motor primitive,' which is a pre-programmed behavior used as a building block for other, more complicated behaviors (Sheridan 1984, Mussa-Ivaldi and Bizzi 2000, Schaal and Atkeson 1998). Each movement is controlled by a series of distinct, overlapping neural mechanisms enacted sequentially. These mechanisms consist of a feedforward movement controller to initiate movement, an online feedback controller to correct the movement in progress, and a separate positional controller to control final endpoint stabilization (Feldman 1980a, b, Humphrey and Reed 1983, Sainburg et al. 1999).

Later studies by Scheidt and Ghez (2007) focused specifically on the movement controller initiating movements and the positional controller that stabilizes the limb at the end of movements. Movements were encouraged to be fast and smooth to prevent evoking online error correction. This was accomplished by using a paradigm of visuomotor adaptation in both point-to-point "reaching" movements (presumed to invoke a sequence of movement → position control actions) and out-and-back reversal movements or "slicing" (presumed to invoke a sequence of movement → movement → position control actions). They found that learned adaptation of reach endpoints within a visuomotor rotation task did not generalize to a similar adaptation of the first "slicing" movement trajectory within the same visuomotor rotation. They also found that adaptation of slicing movement trajectories did not generalize to a difference in the reach endpoint, even though the reach endpoint and the slice turnaround point were co-located. Both of these results suggest that final position (reach endpoint) adapted separately from the movement trajectory (reversal endpoint). These findings suggest that movement trajectory and end effector location are influenced by separate neural control mechanisms.

In support of this idea, Ghez and colleagues (2007) presented evidence that slice reversals and reach endpoints are represented in different reference frames: slice reversals are computed in a hand-centered coordinate frame and reach endpoints are calculated in an eye- or head-centered frame. The idea was further supported by Scheidt and colleagues (2011) who described a single-joint, reach/slice task in which limb impedance was altered at the end of reaching through cued co-activation. Results of this experiment suggest that both reaches and reversals share a common control action to initiate

movement toward a target, but used separate control actions to terminate movement and stabilize the limb at the final target. These studies suggest that the position and movement control actions are the result of separate neural control systems. If separate neural control systems do underlie position and movement control, it stands to reason that injury to one system may not generalize to the other.

Control actions can be differentially impaired after stroke

There is evidence that the movement and positional controllers can be affected differentially by stroke. Scheidt and Stoeckmann (2007) found that all but the most impaired stroke survivors could make feedforward reaching movements in the presence of an unpredictable perturbation, whereas nearly all survivors had marked deficits in their ability to bring the hand to rest at the target. Moreover, participants with impairments in proprioception had greater stabilization deficits (i.e., higher variability at the end of movement) than those with intact proprioception.

Schaefer and colleagues have repeatedly found evidence that movement control and position control during multi-joint reaching tasks in the less-affected, ipsilesional arm, can also be differentially impacted by stroke (Schaefer et al. 2007, 2009a, 2009b, Haaland et al. 2009). They propose a model of laterality of control actions to explain these differences. In their model, lesions in the left hemisphere of the brain contribute to deficits in movement control actions, and lesions in the right hemisphere contribute to deficits in position control. Similarly, another multi-joint reaching experiment performed with the more-impaired, contralesional arm, found that a left hemisphere lesion was associated with degradation of movement trajectory control while a right hemisphere

lesion was associated with degradation of movement termination, i.e., position control (Mani et al. 2013).

Synthesis

Restoration of "normal" motor control is an ideal of stroke rehabilitation and recovery. Effective motor control requires that one be able to formulate and execute a motor plan. To formulate the motor plan, one needs to know the objective of movement as well as the current state of the motor system, and be able to integrate that information to develop a plan for action. In order to execute that motor plan, descending signals from the brain travel to the spinal cord where they act on motoneuron pools and interneuron networks to facilitate activation in task-agonist motoneuron pools and suppress activation of non-necessary motoneuron pools (such as in task-antagonist muscles that are not required for stability). These motoneurons then activate muscles that generate the torques required to move and stabilize the limb.

However, failure at any point in this system compromises ability to perform functional movements. Loss of sensory information impairs knowledge of the current limb state and how it is changing. Loss of the ability to integrate information causes disconnects between the known state, the actions planned, and the action taken. Loss of planning impairs the ability to use information and send useful signals to the spinal cord. Loss of descending pathways cuts off information – excitatory and inhibitory – to neurons in the spinal cord even if a successful movement plan was developed. All of these neural changes also lead to changes in muscle. Muscle can still receive input from motoneurons after stroke, yet can be less able to activate in a functional manner. Muscle

begins to lose mass and shorten; fiber types may shift. Tendons may lengthen and increase slack to compensate for these changes in muscle.

The composite effects of these neural and muscular changes can cause weakness, slowness, loss of smooth movement, and persistent co-activation of muscles, all of which undermine a person's capacity to perform functional movements. Despite decades of effort to develop rehabilitation interventions that can reduce upper extremity impairment and restore functional behavior, there are surprisingly few effective interventions in the upper extremity, and those that do exist are predominantly suitable for a subset of survivors of stroke. In order to understand the limitations of current rehabilitation approaches – and to potentially create new ones – we must better understand these fundamental changes after stroke.

In this Dissertation, I seek to better understand how stroke impacts 1) the coordination of magnitude and timing of an agonist/antagonist muscle pair during targeted force production in the elbow, 2) superposition of movement and position control during point-to-point movements of the elbow, and 3) how changes in these fundamental building blocks of motor control relate to deficits in specific and generalized measures of function and impairment. Given the high levels of variability observed in deficits after stroke, it is important to quantify a broad range of potentially relevant motor and sensory characteristics for each individual to prevent (or account for) confounds observed in experimental performance.

CHAPTER 3: WEAKNESS AND DEFICITS OF ELBOW MUSCLE AGONIST/ ANTAGONIST COORDINATION REDUCE MOTOR FUNCTION AFTER STROKE

After stroke, motor function can be persistently impaired. The ability to produce controlled torques is important for moving the arm. In order to produce controlled torques, one must be able to coordinate the activity of agonist/antagonist muscle pairs in time and in magnitude. In this study, participants with stroke (SP) and neurologically-intact (NI) participants generated and ceased cued, moderate isometric torques at the elbow. We found that SP performance when generating and reducing torques was impaired compared to NI participants. We also found that while participants in both groups could modulate phasic muscle activity to some extent to create torques, SP had elevated levels of co-activation during torque transitions, when holding a torque, and when relaxing compared to NI. Weakness was the only variable found to account for significant variance in impairment of the more-impacted arm, as measured by the upper extremity motor portion of the Fugl-Meyer Assessment. Finally, we found that weakness, speed of torque production, and coordination of agonist/antagonist muscle pairs accounted for significant variance in function of the more-impaired arm, as measured by the Chedoke Arm and Hand Activities Inventory. These findings demonstrate that above and beyond the motor deficits characterized by weakness, deficits in the ability to coordinate flexor and extensor muscles at the elbow correlates significantly with deficits of motor function after stroke.

Introduction

The ability to produce and maintain appropriate levels of torque about joints is critical for performing functional tasks such as lifting and holding a glass of water. This requires that agonist/antagonist muscle groups work together to provide appropriate levels of opposing forces in time. Stroke can impair this ability. A common consequence of stroke is damage to the corticospinal system (primary and secondary motor and somatosensory cortices, subcortical structures, and/or the corticospinal tract), which causes upper extremity (UE) impairments including paresis (weakness), loss of the ability to produce "fractionated" or isolated movement at individual joints, abnormal muscle tone (spasticity) and/or deficits of somatosensation (c.f., Lang et al., 2013).

The specific neural injuries caused by stroke vary from one person to the next, giving rise to a broad range of sensorimotor impairments expressed in the population of survivors (Kunesch et al., 1995). The literature and common clinical experience clearly find that stroke-related impairments contribute significantly to deficits of motor function (Biennerhassett et al., 2007; Hermsdörfer et al., 2003; Wagner et al., 2007; Scheidt and Stoeckmann, 2007; Zackowski et al., 2004), thereby limiting independent living and quality of life (Taub et al., 1993; Tyson et al., 2008). For example, in one study involving a cohort of 104 stroke survivors, Duncan and colleagues report high correlation between a clinical measure of impairment (the UE Fugl-Meyer Motor Assessment) and performance on a clinical assessment of motor function in activities of daily living (the Barthel Index) (Duncan et al., 1992).

However, clinical measures of impairment such as the FM_M are multifaceted tools that quantify several aspects of impairment (e.g., reflex abnormalities, inability to move

in and out of synergy, lack of voluntary wrist and finger motion) and then only with coarse resolution. Similarly, measures of motor function are also multifaceted, in that they assess the ability to perform a variety of tasks simulating everyday activities such as bathing, dressing, eating, and manipulating hand-held objects such as a phone, ruler, or coffee jar. It remains unclear just how much each of the various impairments evaluated by these clinical instruments contributes to stroke-related deficits of motor function.

Many research groups have sought to employ well-controlled laboratory-based motor assessments using high-resolution instrumentation to fill this knowledge gap by characterizing how stroke-related impairments impact specific aspects of neuromotor control, and then how those control deficits impact motor function. As an example, Levin and colleagues describe studies designed to characterize deficits in the regulation of stretch reflex thresholds - a neuromuscular mechanism believed to underlie spasticity and contribute to motor impairment after stroke (Levin et al., 1997; see also Powers et al., 1988; Powers et al., 1989; Kamper et al., 2001) and other brain injuries (Levin et al., 2000). In Levin's study from 2000, elbow kinematics (position and velocity) and electromyographic activity (EMG) were recorded from patients with hemiplegia and neurologically intact individuals during passive and active elbow flexion and extension movements under varying conditions to characterize stretch reflex threshold angles in the arm. The data also allowed the investigators to relate how deficits in the regulation of static stretch reflex thresholds contribute to deficits of active torque production during slow reaching motions. Eleven out of twelve individuals with hemiplegia had static flexor muscle stretch reflex thresholds within the elbow's normal range of motion, giving rise to involuntary muscle activation consistent with hypertonia. One third of participants with

hemiplegia demonstrated this phenomenon in their extensors as well. By contrast, neurologically intact control participants did not have static stretch reflex thresholds within the physiological range of motion.

Participants exhibiting abnormal stretch reflex thresholds also had lower maximal flexor and extensor torques (i.e., greater weakness) when the agonist muscle was in a lengthened position. The range in which reciprocally organized agonist and antagonist muscle activity could be generated was limited in all but one hemiparetic participant. In some hemiparetic participants, ranges were found in which no active torque could be produced in the extensor or either muscle group. These ranges were related to the boundary values of stretch reflex thresholds found during passive muscle stretch, thus establishing a link between deficits of elbow torque production and deficits of motor control revealed in the disorganization of central regulation of individual muscle stretch reflex thresholds. Unfortunately, no attempt was made to link these results to motor function, thus leaving unresolved the question of how joint angle-related deficits of motor control might contribute to deficits of motor function post-stroke.

Taking a different approach, other groups have examined isometric torque production tasks at the elbow (Canning et al 1999; Chang et al. 2013; McCrea 2003) and wrist (Chae et al. 2002) to characterize stroke's impact on neuromuscular coordination, while also controlling for limb motion and the abnormal velocity-dependent reflex responses it can elicit. Two relevant studies found that the more-affected arm is slower both to produce and to relax from the production of cued maximal torques at the elbow (Canning et al. 1999, McCrea et al. 2003), thereby demonstrating that the ability to modulate muscle force in a timely fashion is impaired in chronic stroke. A similar study

of isometric wrist torque control (Chae et al. 2002) also found significantly greater delay in the initiation and termination of muscle contraction in the paretic arm relative to the non-paretic arm after stroke. In that study, delays in initiation and termination of muscle contraction were found to correlate significantly with upper limb motor impairment (as quantified by the UE portion of the Fugl-Meyer Motor Assessment) and physical disability (i.e., deficits of motor function as quantified by the Arm Motor Ability Test).

More recently, Chang and colleagues (2013) recorded intramuscular EMG (iEMG) activity in biceps as chronic stroke survivors performed cued submaximal isometric elbow flexion torques in both limbs. They used the data to examine the relationship between weakness, force variability and spontaneous motor unit discharge. While some spontaneous discharge was observed in resting biceps muscles in both arms of all 10 participating stroke survivors, sustained increases in spontaneous discharge rate were observed after voluntary activation only in the more-involved limb. In this study weakness (not spasticity) was the primary factor interfering with voluntary force control within their small cohort of chronic stroke survivors because the incidence of spontaneous discharge was not related to force variability or weakness. Each of these prior studies report weakness and disordered timing in the activation and deactivation of agonist muscles after stroke, but Chae and colleagues (2002) attempted to relate observed deficits in strength and selective activation of muscles to deficits of motor function. None of these studies evaluated variations in coordination of agonist/antagonist muscle activation magnitude that would be expected to arise closer to – or farther from – the bounds of the joint's range of motion due to joint angle-dependent deficits of stretch reflex regulation as described by Levin and colleagues (2000).

In the current study, we sought to quantify the extent to which position-dependent deficits in the coordination agonist/antagonist muscle activations degrade the ability to produce controlled, goal-directed changes in elbow joint torque after stroke. Survivors of a single unilateral stroke and neurologically intact control participants performed a set of experimental tasks wherein they were required to quickly and accurately produce, hold, and release targeted, submaximal isometric elbow flexion and extension torques. We analyzed elbow torque signals and EMG activities recorded from primary elbow flexor and extensor muscles when the tasks were performed with the elbow fixed in 3 different flexed positions within the middle of its range. We hypothesized that position-dependent deficits of agonist/antagonist coordination correlate significantly to clinical measures of motor impairment and functional deficits after stroke. To that end, we used stepwise forward regression analysis to assess the extent to which differences in performance on composite clinical measures of motor impairment (i.e., the upper extremity component of the Fugl-Meyer Motor Assessment) and motor function (i.e., Chedoke Arm and Hand Activity Inventory) correlate with measures of neuromuscular coordination derived from performances in the isometric torque task.

Methods

Participants

Twenty-three adults provided written informed consent to participate in this study in compliance with policies established by the Marquette University Institutional Review Board (protocol number HR-1507). Thirteen of the participants were survivors of unilateral stroke (SP) (5 female; 34 to 70 years of age), and ten were age-range matched

neurologically-intact (NI) controls (4 female; 49 to 76 years of age; see Table 3.1). All SP were more than 6 months post-stroke, demonstrated motor deficits at time of testing, and were able to perform the task comfortably. Exclusion criteria included: inability to follow two-step instructions (assessed during participant screening); inability to place the arm within 20˚ of the horizontal plane while supported (or experiencing pain in that position); fixed contracture or a history of tendon transfer; profound atrophy of muscles in the target area(s) of testing; history of a bleeding disorder, myasthenia gravis, amyotrophic lateral sclerosis or any other disease that might interfere with neuromuscular function. Medical records were solicited for all SP to verify lesion location and type. Although we did not exclude participants based on recent botulinum neurotoxin therapy (three participants had received injections within three months of participation, noted in Table 3.1), none had received injections in the month prior to experimental testing. We asked participants to perform isometric torque-tracking tasks. Data collection occurred in a single experimental session lasting about 2 hours, including setup. SP used the more-involved arm to perform the tasks, whereas NI used the arm reported as dominant.

Table 3. 1Participant characteristics

Group	ID	Age	Sex	Test Hand	Dom. Hand	Flx. Musc	Ext. Musc	Avg. Max. τ (Nm)	FMM	CAHAI	FMP	MAS	MoCA	Years since stroke	Lesion Type	Lesion Location
NI	1	62	M	R	R	BIL	TLG	51.7	*	*	*	*	*	*	*	*
NI	2	62	F	R	R	BIS	TLT	22.6	*	*	*	*	*	*	*	*
NI	3	60	M	R	R	BIS	TLT	30.3	*	*	*	*	*	*	*	*
NI	4	63	F	R	R	BRD	TLG	20.3	*	*	*	*	*	*	*	*
NI	5	72	M	R	R	BIS	TLT	30.3	*	*	*	*	*	*	*	*
NI	6	66	F	R	R	BIS	TLG	32.6	*	*	*	*	*	*	*	*
NI	7	70	M	R	R	BIS	TLG	58.3	*	*	*	*	*	*	*	*
NI	8	76	M	R	R	BIS	TLT	46.9	*	*	*	*	*	*	*	*
NI	9	51	F	R	R	BRD	TLG	28.6	*	*	*	*	*	*	*	*
SP	101‡	57	M	L	R	BRD	TLG	17.3	27	18	3	1.5	27	12	I	R: Midbrain
SP	102‡	59	M	R	R	BIS	TLG	27.9	20	24	8	4	26†	7	I	L: MCA, BG, Insular Cortex
SP	103	65	F	L	R	BRD	TLG	7.0	30	23	8	6	26	29	I	R: **
SP	104‡	52	M	R	R	BIS	TLG	8.8	21	23	8	3.5	23†	13	**	L: **
SP	106‡	64	F	R	R	BIS	TLG	12.5	45	32	4	2	14†	24	**	L: **
SP	107‡	61	M	R	R	BIS	TLG	13.0	27	15	2	2.5	10†	12	I	L: MCA Distribution
SP	108	61	M	L	R	BIL	TRT	6.2	9	14	5	3	28	9	I	R: Frontal/Temporal/Parietal
SP	110	62	M	L	R	BIS	TLG	25.6	41	63	8	4.5	23	7	I	R: BG & Caudate
SP	111‡	69	F	R	R	BIS	TLT	9.3	23	46	8	3	25	35	H	L: PCA
SP	112	34	M	L	L	BIS	TLG	15.9	21	23	5	4.5	27	6	H	R:
SP	113	63	F	L	R	BIS	TLG	24.8	37	52	5	3.5	22	10	**	R: **
SP	114	64	M	L	R	BRD	TLG	35.8	66	90	8	0	24	7	I	R: Multi-focal Periventricular White Matter
SP	115	70	F	L	L	BIS	TLT	16.6	32	30	8	1.5	22	13	H	R

NI: neurologically intact; SP: stroke participant; M: male; F: female; R: right; L: left; DOM: dominant; Flx Musc: Flexor selected, BIL: long biceps, BIS: short biceps, BRD: brachioradialis. Ext. Mus: Selected extensor, TLG: long triceps, TLT, lateral triceps. τ: torque. FMM: upper extremity motor portion of Fugl-Meyer Assessment. CAHAI: Chedoke Arm and Hand Activities Inventory. FMP: upper extremity proprioception portion of sensory subsection of Fugl-Meyer Assessment. MAS: Modified Ashworth Scale. MoCA: Montreal Cognitive Assessment. I: ischemic, H: hemorrhagic. R: right hemisphere, L: left hemisphere. MCA: middle cerebral artery, PCA: posterior cerebral artery, BG: basal ganglia. ‡ expressive aphasia; ** medical records not available

Clinical Assessments

All SP were initially evaluated by the same physical therapist who assessed sensorimotor function (Table 3.1). Upper extremity impairment was evaluated using the motor and sensory subtests of the Fugl-Meyer assessment (FMA; Fugl-Meyer et al. 1975). The motor portion of the FMA (FM_M) assesses reflexes and stages of coordinated movement with a total score range from 0 to 66, where 0 indicates a complete lack of reflexes or volitional movement and 66 indicates intact reflexes, and arm/hand movements. The sensory portion of the FMA includes a coarse test of proprioceptive integrity (the clinical "*up or down?*" test; DeGowin et al., 1987; Epstein et al., 2008), which assesses proprioceptive discrimination at the shoulder, elbow, wrist and thumb. Here, the clinician asks the participant to close their eyes, moves the tested joint up and down several times, and when the joint stops moving, the participant is asked to indicate joint orientation (up or down). Six repetitions were performed at each joint. If the response was brisk and accurate with no errors, proprioception at that joint was rated "intact" and scored as a 2; if the participant was unable to respond with confidence and/or they made 1 error, proprioception at the joint was rated "impaired" and scored a 1; if the participant was unable to determine position and/or made 2 or more errors, proprioception at the joint was rated "absent" and scored a 0. Scores were summed across joints to give a maximum possible score of 8. Results of the "*up or down?*" test were corroborated using a robotic test of proprioceptive integrity that uses ascending and descending amounts of mechanical perturbation to the hand in order to quantify an individual's movement detection threshold, described previously (Mrotek et al., 2017).

We assessed muscle tone at the elbow using the Modified Ashworth scale (MAS; Bohannon and Smith 1987). The MAS grades flexor and extensor muscle tone about the joint on a scale that ranges from 0 to 4, where a 0 indicates no increase in tone compared to the less-affected arm and a 4 indicates tone so severe as to render the arm rigid. To obtain an overall estimate of spasticity at the elbow, MAS scores were averaged across the elbow flexors and extensors. We screened for cognitive impairments using the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). The MoCA was designed to detect impairment of short-term memory recall, visuospatial information processing, executive function, attention, working memory, and language. MoCA scores ≥ 26 on a 30-point scale are considered normal whereas scores ≤ 25 suggest cognitive impairment. We used the 13-item Chedoke Arm and Hand Activity Inventory (CAHAI; Barecca et al. 2005) to assess function in the more affected limb during bimanual activities of daily living such as pouring a glass of water and buttoning a shirt. Individual assessments on the CAHAI score from 1 to 7, giving a maximum possible total of 91 points. An item score of 1 indicates that the participant could not perform the task whereas a score of 7 indicates that the more affected arm was used fully and efficiently in the bimanual task. Results are summarized in Table 3.1.

Experimental Setup

Participants were seated in a high-backed chair with the test arm rigidly coupled to a custom fixture mounted to a 6-degree-of-freedom load cell (model 75E20A4-I125-AF, JR3, Woodland, CA), which was mounted on a Biodex dynamometer (Biodex System 3, Biodex Inc., Shirley, NY). The torso was securely strapped to the chair with

Velcro straps to minimize trunk motion. The arm was oriented palm downward with the elbow's center of rotation aligned to that of the dynamometer. Seat location was adjusted such that the upper arm was abducted to within 20º of horizontal, and shoulder horizontal flexion was less than 20º. During testing, the dynamometer was used to rotate the elbow into each of three predefined positions: a "neutral" position (N, with the forearm flexed 90º relative to the upper arm), a flexed position (F, neutral +25º), and an extended position (E, neutral -25º; Fig 3.1A). Elbow flexion/extension torque signals from the load cell were low-pass filtered using a passive, 1st-order, 300 Hz hardware filter, prior to digitization at a rate of 1000 samples per second.

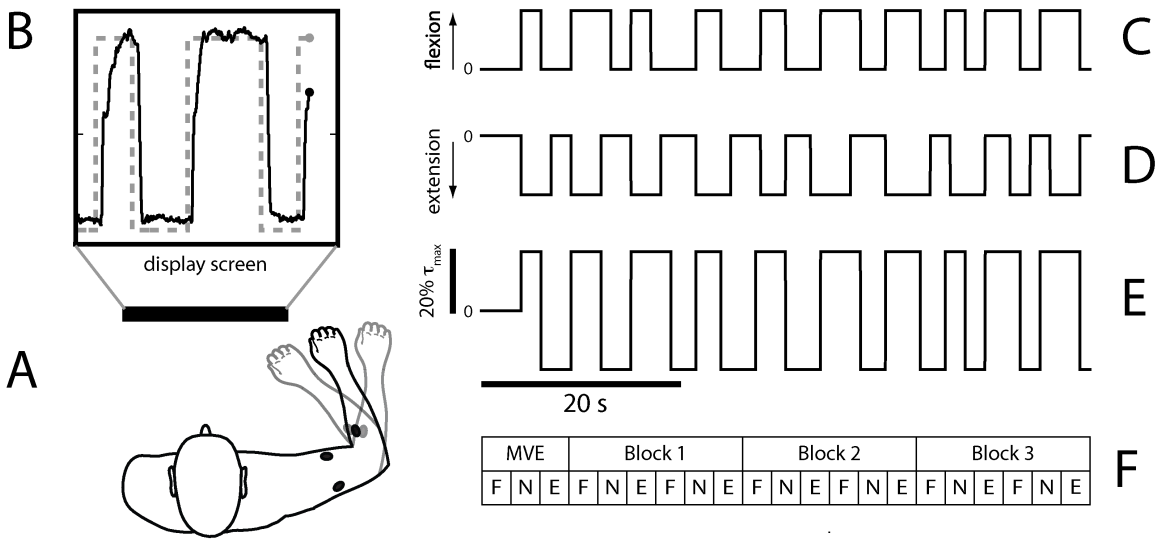

Figure 3.1: Experiment setup and procedure. A: Participants viewed a scrolling digital display with a discrete-transition torque target (B, gray) and real-time elbow torque feedback (B, black). All torque targets were set at 20% τ_{max} for torque production or resting baseline for relax cues. A: Participants sat upright with the arm locked in each of three positions: neutral, N (90° elbow flexion); flexed, F (N - 25°); and extended, E (N + 25°). EMG signals were recorded from elbow flexors and extensors. C-E: Participants performed three tasks: a flex/relax task (C), an extend/relax task (D), and a flex/extend task (E), horizontal bar represents 20 seconds, vertical bar represents 20% AMT. F: Participants performed MVIC collection followed by each of the three tasks repeated twice in each of the three positions. Order of positions and discrete transition blocks were randomized across participants.

Surface EMG was recorded from three elbow flexor muscles (BICS: short head of biceps; BICL: long head of biceps; BRD: brachioradialis) and two elbow extensor muscles (TRILT and TRILG: lateral and long heads of triceps, respectively). EMG signals were band-pass filtered with an active, 20-450 Hz filter and amplified with a gain of 1000 (Bagnoli-8, Delsys Inc., Natick, MA) prior to digitization at a rate of 1000 samples per second.

Experimental Tasks

Each participant performed four different isometric, goal-directed elbow torque production tasks while viewing a vertical display screen showing two scrolling traces (target and feedback cursors) moving across the screen at a rate of 2.5 cm/s. The torque target - represented by the dashed gray line in Fig. 3.1B - corresponded to the instantaneous value of elbow flexion/extension torque participants were instructed to produce. Upward deviations represented flexion torque, and downward deviations represented extension. The torque cursor (represented by the black trace in Fig. 3.1B) corresponded to the instantaneous elbow flexion/extension torque actually generated by the participant as measured by the load cell. Additional details of the visual display varied by task type, as described below.

The first task (the "maximum voluntary exertion" task, MVE) was designed to identify each individual's maximal capacity to produce elbow flexion and extension torques, τ_{max}, which were used to specify participant-specific torque production goals for the remaining tasks. Participants performed three sets of four, 10 s maximal exertion trials with one set in each of the three elbow positions (flexed, neutral, extended). Each set consisted of two flexion and two extension trials with a five second break between trials. In each trial, participants attempted to track a torque target that increased from relax at a rate of 6 N-m/sec and ultimately surpassed their maximal torque generation abilities. During each trial, participants were strongly encouraged to exert themselves to the point of failure. Upon completing this task, we extracted the maximal voluntary elbow flexion and extension torques, as well as maximal voluntary isometric contraction EMGs (MVIC EMGs) from their data. We then identified 20% of the maximal measured

torque magnitude averaged across the flexion and extension conditions for all positions (i.e., 20% of the average τ_{max}) as the torque target for each participant for the subsequent tasks.

For the two primary experimental tasks, participants were instructed to track discrete, step-wise changes in target torque that involved cued torque production in one direction only (flexion or extension), alternating with cued "relaxation" back to the baseline level of torque measured immediately prior to trial onset. These tasks allowed us to assess each participant's ability to produce rapid changes in isometric elbow joint torque in each of the three joint positions. One task, the *Flex/Relax* task, involved the production of cued flexion torques from relaxation (F_R) and cued relaxation after the production of flexion torque (R_F; Fig 3.1C). The *Extend/Relax* task involved extension torque production from the "relaxed" state (E_R) and relaxation after extension torque production (R_E; Fig 3.1D). For both primary tasks, each 60 s trial included 20 cued transitions between states (10 in each direction), with a 200 ms auditory tone coincident with the visual cue transitions. Flexion was cued by a 440 Hz tone, relaxation by a 700 Hz tone, and Extension by a 1110 Hz tone. In each case, the inter-cue interval was pseudorandomly distributed, such that transition times (2.9 ± 0.75 s; mean ± 1 SD) were unpredictable but identical across participants. Participants were instructed to: "Match the elbow torque cursor to the target trace as quickly and as accurately as possible." Each task was performed twice at each elbow position; the order of tasks was randomized across participants to minimize potential order effects (an example is shown in Fig. 3.1F).

During pilot testing, we observed that stroke survivors consistently exhibited limitations in their ability to produce rapid changes in elbow joint torque. We therefore

asked each participant in this study to also perform a third variant of the step-tracking task (the *Flex/Extend* or "reciprocal" task). This supplemental experimental task was designed to test whether performance limitations observed during the primary experimental tasks reflected hard constraints (i.e., whether the participant could never exceed the rates of torque production observed in the *Flex/Relax* and *Extend/Relax* tasks) or whether the limitations were due to context-specific constraints on neuromotor control. The *Flex/Extend* task required generating a cued, goal-directed flexion torque after holding a steady-state extension torque (F_E), and *vice versa* (E_F), at each of the three elbow joint positions without intervening relaxation periods (Fig 3.1E). The timing and presentation of torque transition cues was the same as that described for the main torque tracking tasks.

Data Analysis

Digitized torque signals from the load cell were subsequently low-pass filtered with a 6th-order, zero-lag Butterworth filter (5 Hz cutoff frequency), and then divided by the participant's average τ_{max} to yield a normalized measure of biomechanical performance, which controls for inter-participant differences in strength. The first three time derivatives of the normalized torque signal (which we refer to as $\dot{\boldsymbol{\tau}}$, $\ddot{\boldsymbol{\tau}}$, and $\dddot{\boldsymbol{\tau}}$) were calculated and examined within the 2.5 s interval immediately following cue presentation. For each transition, we identified the rate of torque change when it reached its peak value ($\dot{\boldsymbol{\tau}}_{peak}$) and the time when this occurred (t_{peak}; refer to the vertical dashed lines in Figs 3.2A and 3.2B). We then defined the *transition start time* (t_{start}) as the instant preceding $t_{peak}$when $\dot{\tau}$ first reached 10% of $\dot{\tau}_{peak}$. We defined *transition end time*

(t_{end}) as the moment after $t_{peak}$when $\dot{\boldsymbol{\tau}}$ first fell below 10% of $\dot{\tau}_{peak}$. (t_{start} and t_{end} are represented by vertical dotted lines in Figs 3.2A and 3.2B.) We also defined the *target hold period* as the time between transitions during which participants were to maintain a steady target torque at either the 20% maximal torque target or the baseline resting target (specifically, from t_{end} + 500 ms to the t_{start} of the following transition; large horizontal gray boxes in Figs 3.2A and 3.2B).

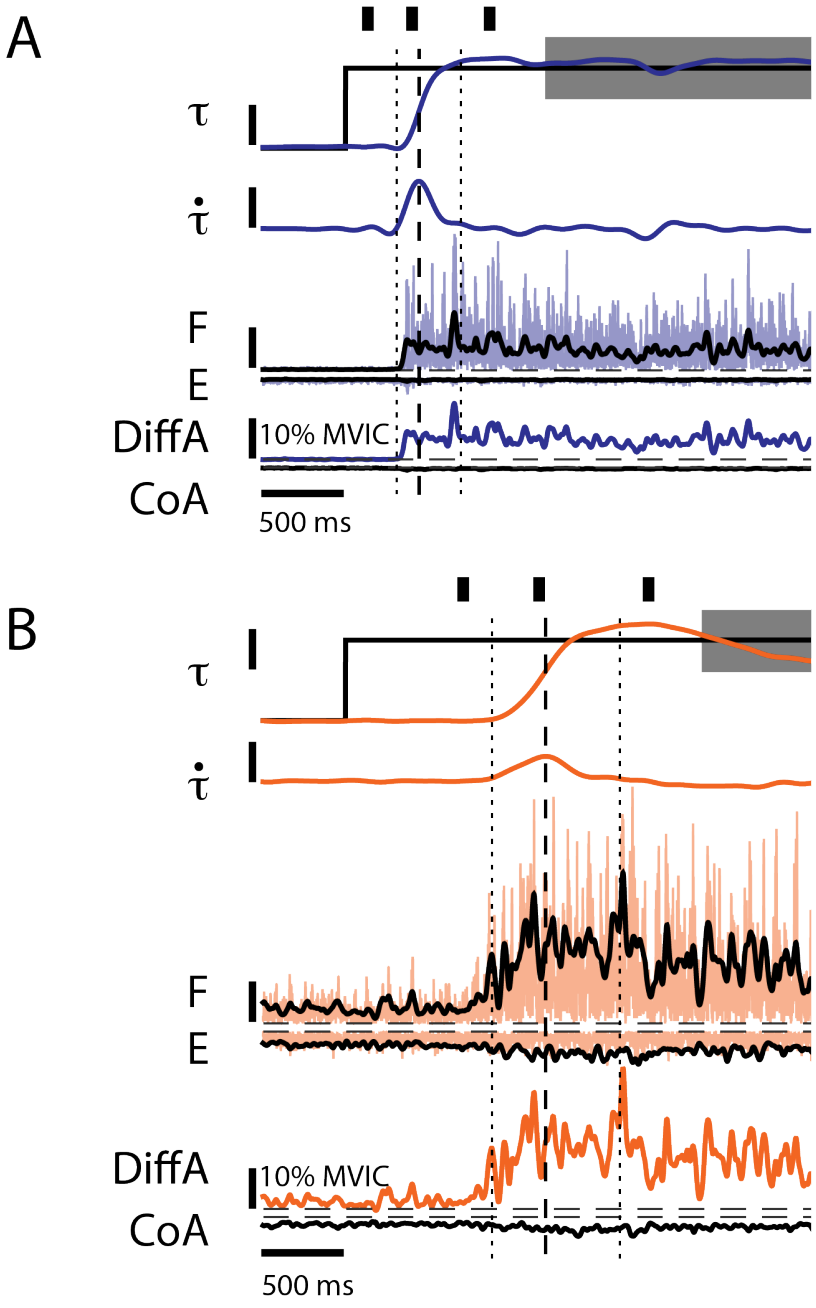

Figure 3.2: Discrete torque tracking task performance for one transition in one NI (A) and one SP (B) participant. τ: torque target (20% τ_{max}, black) and the participant's torque production (blue (A), orange (B), vertical scale bar indicates 10% τ_{max}). $\dot{\boldsymbol{\tau}}$ first time-derivative of torque (blue (A), orange (B), vertical scale bar indicates 100% τ_{max} per second) was used to derive three time points (vertical dashed lines): $\dot{\tau}_{peak}$ (center), transition start (10% $\dot{\tau}_{peak}$, left), and transition stop (10% $\dot{\tau}_{peak}$, right). The gray box immediately prior to $\dot{\tau}_{peak}$ is the 50 ms window used to evaluate EMG during the transition. F: Raw (blue (A), orange (B)) and processed (black) normalized flexor activity, vertical scale bar indicates 10% MVIC. Horizontal dashed line indicates 0% MVIC in all EMG and EMG-derived measures. E: Raw (blue (A), orange (B)) and processed (black) normalized extensor activity. DiffA: Difference activity (blue (A), orange (B). CoA: Co-activity (black), vertical scale bar indicates 10% MVIC. Horizontal scale bar shows 500 ms.

Prior observations of goal-directed reaching have indicated that stroke survivors may be slower to react and to execute movement, movements may lack smoothness, and accuracy of target capture and hold may be impaired (Trombly 1992; Cirstea and Levin 2000). We defined five torque performance measures to quantify similar aspects of isometric torque production in these goal-directed tasks. First, we computed reaction time (RT) as the amount of time between transition cue and t_{start}. Two additional measures pertained to performance during the transition (i.e., prior to t_{end}): We defined *Execution Time (ET)* as the time between t_{start} and t_{end}; Within the execution window, we quantified the relative smoothness of torque production using a *Jerk Index (JI*; dimensionless integrated squared jerk) previously described by Hogan and Sternad (2009):

$$Jerk\ Index = \frac{(t_{end}-t_{start})^3}{\dot{\tau}_{peak}^2}\int_{t_{start}}^{t_{end}} \ddot{\tau}^2(t)dt \qquad \text{[Eq. 1]}$$

This performance measure is sensitive to variations in the shape of the torque trajectory while remaining insensitive to variations in execution time and peak rate of torque change. The remaining two measures quantified performance after the end of transition. We quantified the ability to accurately produce a desired level of elbow torque by computing *Target Capture Error Magnitude* ($|\varepsilon_{end}|$), defined as the absolute magnitude of the difference between torque produced at t_{end} and the specified target value. Finally, to quantify the participant's ability to maintain a desired level of sustained torque, we defined *Hold Variability* (σ_{hold}) as the standard deviation of the measured torque signal during the hold period. Individual transitions were excluded from analysis if the participant attempted transitions in advance of the cue, or if $\dot{\boldsymbol{\tau}}_{peak}$ was not in the cued direction.

All digitized EMG signals were notch filtered at 60, 120 and 180 Hz, (±10 Hz) using a 3rd-order, zero-lag Butterworth filter to remove line-noise interference. All EMG signals were then zero-meaned, rectified, and filtered with a 20 Hz low-pass, 2nd-order zero-lag Butterworth filter. EMG signals from maximal isometric torque production tasks were further filtered with a 100 ms, moving average filter and the maximal value (i.e., MVIC) was used as a normalization factor for the EMG signals from each respective muscle. For each muscle and for each individual trial, the processed EMG signal was then normalized to (i.e., divided by) the maximal value obtained for that muscle.

For each participant, we selected a "primary flexor" and a "primary extensor" for detailed statistical analysis. These muscles were the elbow flexor and the elbow extensor muscles wherein EMG activities exhibited the greatest peak cross-correlation with the elbow flexion or extension torques (respectively) that were recorded during MVE trials. As listed in Table 3.1, the selected muscles varied across participants in both groups.

Secondary measures of agonist/antagonist muscle coordination were calculated using EMG activities from the identified primary flexor and extensors. We estimated the amount of "wasted activation" (c.f., Thoroughman and Shadmehr, 2000) during isometric torque production by calculating a measure of instantaneous co-activation (CoA):

$$CoA(t) = \min\left[flexor(t), extensor(t)\right]. \qquad \text{[Eq. 2]}$$

CoA(t) represents the magnitude of normalized EMG activity that is approximately equal and opposite in the antagonist muscle pair. We then quantified each participant's ability to differentially activate these muscles by calculating a measure of difference-activation (DiffA):

$$DiffA(t) = flexor(t) - extensor(t). \qquad \text{[Eq. 3]}$$

DiffA(t) quantifies the instantaneous amount of phasic activation across the antagonist muscle pair during isometric torque production. We used these CoA and DiffA to quantify instantaneous coordination of activation magnitude between the selected elbow flexor and extensor. We defined three, 50-ms time periods of interest over which we calculated average EMG activity for the primary elbow flexor and extensor, as well as the average CoA and DiffA measures derived from those EMG activities. To characterize muscle coordination during transitions between cued levels of elbow torque, we defined a 50-ms window immediately prior to $\dot{\boldsymbol{\tau}}_{peak}$ (short horizontal black bars at the top of Figs 3.2A and 3.2B). To characterize muscle coordination while participants maintained steady levels of cued torque (i.e., flexion, extension, relaxed), we defined another window starting 150 ms after the end of transition, (short horizontal gray bars at the top of Figs 3.2A and 3.2B). We also characterized "baseline" levels of muscle activity when participants were to supposed to be relaxed starting 200 ms prior to transition start in all trial types including a movement control action.

Statistical Hypothesis Testing

The current study had two specific objectives. The first was to quantify the extent to which arm position-dependent deficits in agonist/antagonist muscle coordination degrade the ability to produce controlled, goal-directed changes in elbow joint torque after stroke. The second was to test the hypothesis that stroke-related deficits of agonist/antagonist coordination are significantly correlated with motor impairment and deficits of motor function. To address the first objective, we compared the ability of NI and SP to perform four different, isometric elbow torque transitions $\{F_R, R_F, E_R, R_E\}$ in

each of three different elbow positions {*flexed, neutral, extended*}. Due to the broad range of impairment and considerable variability represented within our small cohort of stroke survivors, we employed the nonparametric inverse normal transform (INT; Leupson 2016) rank transform (RT Type 1; Conover and Iman 1981; see also Laczko et al. 2017) as our primary statistical analysis approach. In the INT-RT1 test, the entire set of observations for a given dependent variable is first ranked from smallest to largest, with the smallest observation having rank 1, the second smallest rank 2, and so on (average ranks are assigned in the case of ties). Next, ranks are standardized by computing their normalized ranks:

$$INT = \Phi^{-1}(R_i/(n+1)),$$

where R_i are the ranks of the dependent variable, n is the number of observations and Φ^{-1} is the inverse normal transformation. Finally, a parametric F test [mixed model repeated measures analysis of variance (ANOVA)] is applied to the INT standardized ranks. The INT-RT1 analysis takes advantage of both between and within block information, resulting in a distribution-free test that compares favorably with the Friedman test and Fischer's randomization test in terms of robustness and power (Leupson 2016, Conover and Iman 1981), and has also been shown to be acceptable for assessing interactions between factors (Conover and Iman 1981).

To achieve our first objective, we planned to use INT-RT1 ANOVA and post-hoc Bonferroni t-test to examine the main effects of participant group {SP, NIC}, transition type *{F_R, R_F, E_R, R_E},* and elbow joint position {*flexed, neutral, extended*} on each of five torque performance variables $\{|\dot{\tau}_{peak}|, ET, JI, |\varepsilon_{end}|, \sigma_{hold}\}$. We expected that position-related deficits in the ability to produce controlled, goal-directed changes in elbow joint

torque post-stroke would manifest as three-way interactions between joint position, transition type and participant group. In the absence of three-way interactions, two-way interactions between group and transition type would suggest that stroke-related coordination deficits in our isometric task do not depend substantially on elbow joint position.

We next planned to use paired t-test to analyze INT-RT1 $\left|\dot{\tau}_{peak}\right|$ values from the supplemental *Flex/Extend* task transitions to determine whether torque production limitations in the primary experimental tasks were due to fixed constraints on the rate of muscular torque production, or whether observed limitations were due to context-specific constraints on neuromotor control. We specifically compared whether normalized $\left|\dot{\tau}_{peak}\right|$ values produced in the F_E and E_F transitions could exceed those produced by the same participants during F_R and E_R transitions. A positive result in the SP group would suggest that torque production limitations exhibited by stroke survivors in the primary experimental tasks were in fact due to context-specific constraints on neuromotor control rather than on fixed neuromuscular constraints on the rate of muscular torque production.

We next planned to use INT-RT1 ANOVA and post-hoc Bonferroni t-test to examine the main effects of participant group {SP, NIC}, transition type *{F_R, R_F, E_R, R_E}*, and elbow joint position {*flexed, neutral, extended*} on measures of neuromuscular coordination. We analyzed measures of flexor/extensor coordination (CoA and DiffA), and the muscle activation patterns that contribute to them [FLeXor activity (FLX); EXTensor activity (EXT)], during torque transitions (i.e., within the 50 ms window immediately preceding t_{peak}) and during maintenance of the acquired torque (i.e., from t_{end}+150 to t_{end}+200). We were particularly interested in the extent to which these

measures varied across participant group {SP, NIC}, transition type *{F_R, R_F, E_R, R_E}*, and elbow joint position {*flexed, neutral, extended*} and the extent to which they might explain variations in the performance variables derived from the isometric torque signals.

Finally, we tested the hypothesis that deficits of agonist/antagonist coordination correlate significantly with motor impairment and deficits of motor function after stroke using stepwise forward linear multiple regression analysis (Kachigan 1986; c.f., Harris and Eng 2007; Wagner et al. 2007). The first set of forward regressions sought to determine the extent to which specific impairments correlated with performance in the goal-directed isometric torque production task. In these analyses, specific impairment measures were used as input variables (e.g., τ_{max}, MAS, MoCA, FM_{LT}, and AMDT scores) to model selected response variables that describe participant performance during torque transition ($|\dot{\tau}_{peak}|$) and after torque target capture (σ_{hold}). A second set of forward regression analyses sought to determine the extent to which broad measures of upper extremity function and impairment were explained by task performance, muscle coordination and specific impairments. In these analyses, the input measures included performance measures during the primary Flex/Relax and Extend/Relax tasks (i.e., $|\dot{\tau}_{peak}|$, *ET*, *JI*, $|\varepsilon_{end}|$, σ_{hold}, CoA_{Tpeak}, CoA_{Tend}, $DiffA_{Tpeak}$, and $DiffA_{Tend}$) and specific measures of impairment (e.g., τ_{max}, MAS, AMDT, FM_{LT}, MoCA); response variables included composite measures of upper extremity function (CAHAI) and impairment (FM_M).

All statistical testing was performed within the SPSS computing environment (IBM Corp, Released 2012). Corrections for multiple comparisons were employed such that statistical effects were considered significant using a family-wise error rate of α =

0.05. Data are reported as means ± SD within the text and displayed as means ± SE in the figures.

Results

The ability to initiate, maintain, and cease production of moderate (20% of average maximal) elbow flexion/extension torque was tested in 13 hemiparetic survivors of stroke and 10 neurologically-intact controls across three elbow joint angles. All participants were attentive and engaged in the tasks, and all attempted to follow task instructions during the experimental sessions. Within each trial (Figs 3.1C-3.1E), a torque transition was considered "good" if it was initiated after a minimum reaction time of 0.1 s and it was performed in the cued direction. Although performance varied considerably within the SP group, all participants excepting S108 were able to successfully perform all four tasks in all three elbow joint positions demonstrating that motor planning was preserved in these participants. S108 successfully performed the tasks when the elbow was flexed and in the neutral position, but failed to execute any valid torque transitions when the elbow was extended. Reaction times averaged 0.268 ± 0.062 s for NI participants and 0.471 ± 0.145 s for SP participants. Across all SP, 17.9% of transitions were excluded because the participant attempted transitions in advance of the cue or because $\dot{\boldsymbol{\tau}}_{peak}$ was not in the cued direction. By contrast, the failure rate was 2.6% for NI participants. Within the SP group, reaction times were not significantly correlated with overall MoCA scores (Pearson's $r = 0.041$, $p = 0.895$). A hardware error compromised the magnitude of recorded torques during testing of one NI participant (NI_{10}); this participant's data were excluded from subsequent analysis. An EMG electrode came

loose during testing of another NI participant (NI_3); this participant's EMG data from the affected trials were excluded from analysis. Finally, one stroke survivor (SP_{115}) did not complete the *Flex/Extend* task, and was not included in analysis of that task's performance.

MVE task performance

In agreement with prior studies of isometric elbow torque production (Canning et al 1999; Chang et al., 2013; McCrea, 2003), average maximal torques (τ_{max}) were dramatically lower in the SP group as compared to the NI group [NI: τ_{max} = 35.7 ± 13.32 Nm, range {20.3, 58.3}; SP: τ_{max} = 17.0 ± 9.1 Nm, range {6.2, 35.8}]. Within the SP group, τ_{max} was positively correlated with both FM_M (Pearson's r = 0.657; p=0.015, N=13) and CAHAI (r = 0.723; p=0.005, N=13). Therefore, to present each participant with torque targets that required comparable effort, we defined individualized torque targets for the remaining three experimental tasks as 20% of each individual's average τ_{max} values.

Primary experimental task performance

Performance measures in the primary experimental task suggest that position-dependent neuromotor impairments did not impact the ability to produce goal-directed changes in isometric elbow torque. As we shall show, variations in performance were instead largely dependent on whether a participant had had a stroke, and whether they were attempting to generate elbow torque or relax from torque generation. We used separate, mixed-model, repeated measures, INT-RT1 ANOVA and post-hoc Bonferroni t-

test to examine the main and interaction effects of participant group {SP, NI}, transition type *{F_R, R_F, E_R, R_E},* and elbow joint position {*flexed, neutral, extended*} on each of the five torque performance variables: {$|\dot{\tau}_{peak}|$, *ET*, *JI*, $|\varepsilon_{end}|$, σ_{hold}}. We observed a consistent main effect of group across all five performance variables ($F_{(1, 216)} \geq 182.199$ and $p < 0.0005$ in all cases) and transition type ($F_{(3, 216)} \geq 4.483$ and $p \leq 0.004$ in all cases), but not of elbow joint position ($F_{(2, 216)} \leq 1.452$ and $p \geq 0.236$ in all cases). Although we observed consistent interaction between group and transition type ($F_{(3, 216)} \geq 4.165$, $p \leq 0.007$ in all cases, discussed further in the coming paragraphs), we found no evidence of a three-way interaction between group, transition type and position ($F_{(12,216)} \leq 1.410$ and $p \geq 0.163$) in any case.

Across all performance variables, the main effect of group adhered to expectations with the SP group demonstrating impairments in performing transitions between targeted torque levels and sustaining targeted torques compared with NI controls (Fig 3.3). Compared to the NI group, SP made torque transitions that were slower (NI: $|\dot{\tau}_{peak}|$ = 108 ± 21 %τ_{max}/s; SP: $|\dot{\tau}_{peak}|$ = 60 ± 21 %τ_{max}/s) and of longer duration (NI: *ET* = 0.367 ± 0.068 s; SP: *ET* = 0.695 ± 0.151 s), less smooth (NI: *JI* = 168 ± 77; SP: *JI* = 1471 ± 1119), less accurate upon target capture (NI: $|\varepsilon_{end}|$ = 1.1 ± 0.3 %τ_{max}; SP: $|\varepsilon_{end}|$ = 7.6 ± 4.8 %τ_{max}), and more variable during the hold interval (NI: σ_{hold} = 0.4 ± 0.1 %τ_{max}; SP: σ_{hold} = 1.3 ± 0.8 %τ_{max}).

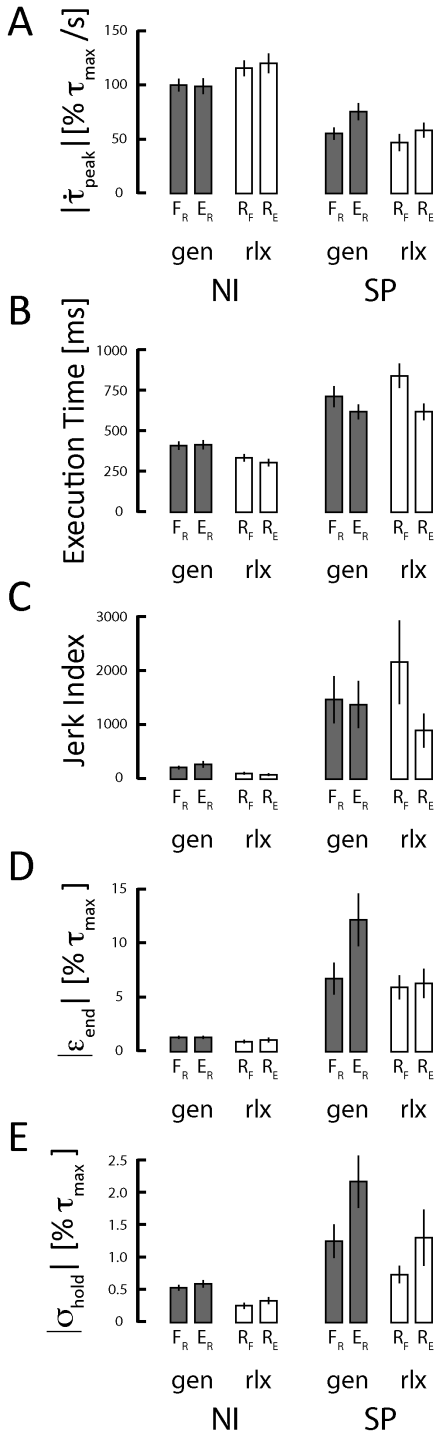

Figure 3.3: Kinetic performance of NI and SP in step-torque tracking task. Gray bars, generating torque (Flex from relax, Extend from relax; white bars, relaxing from torque production (Relax from flex, Relax from extend). Error bars are ± 1 S.E.M. A: peak rate of torque change during transition. B: Execution time to complete transition. C: Dimensionless jerkiness of torque transition. D: Target error at end of torque transition. E: Hold variability during steady state hold of torque or relaxation.

As we describe below, ANOVA also revealed main effects of transition type for all performance variables and interactions between group and transition type for all performance variables. The NI group expressed consistent performance dependencies on transition type (torque production vs. relaxation) regardless of task (Flex/Relax vs. Extend/Relax), therefore we first describe the main effect of transition type as it was present within the NI group. We then describe how SP participants deviated from that "normal" pattern of results using post-hoc paired t-test where appropriate. When describing the transition type differences for the NI group, we collapsed across tasks, i.e., $\{F_R, E_R\}$ and $\{R_F, R_E\}$, prior to performing post-hoc t-tests. As SP performance was less consistent across task- and trial-types, behavior was not collapsed across task prior to performing post-hoc t-tests in the SP group.

NI participants had a faster peak rate of torque change when relaxing than when generating torque; SP participants demonstrated the opposite pattern (Fig. 3.3A). We observed a main effect of transition type on $\left|\dot{\tau}_{peak}\right|$ depending on whether participants were producing torque from rest or relaxing from torque production ($F_{(3,216)} = 4.483$, $p = 0.004$). NI exhibited faster rates of torque change when relaxing vs. producing torques ($T_8 = 5.351$; $p = 0.001$). SP exhibited slower rates of torque change when relaxing vs. producing elbow torques ($T_{12} = 2.938$; $p = 0.012$). Additionally, SP exhibited lower $\left|\dot{\tau}_{peak}\right|$ values in the *Flex/Relax* task than in the *Extend/Relax* task ($T_{12} = 3.113$; $p = 0.009$).

The pattern of results observed for $\left|\dot{\tau}_{peak}\right|$ was also reflected in transition execution times and Jerk indices (i.e., transition smoothness). NI participants took less time to relax than to generate torques, while SP participants took as long or longer to

relax than to generate torques (Fig. 3.3B). We observed a main effect of transition type on ET ($F_{(3,216)} = 14.057$, $p < 0.0005$), as well as an interaction between group and transition type ($F_{(3,216)} = 12.020$, $p < 0.0005$). For the NI group, ETs were shorter when relaxing vs. generating torques in both tasks ($T_8 = 5.22$; $p = 0.001$). By contrast, SP took as long or longer to relax after actively generating flexion torque (in the *Flex/Relax* task; R_F vs. F_R), and about as long to relax after generating extension torque (in the *Extend/Relax* task; R_E vs. E_R). Moreover, SP participants exhibited longer execution times on average in the *Flex/Relax* task than in the *Extend/Relax* task ($T_{12} = 2.758$; $p = 0.017$).

SP made jerkier transitions than NI, which was most pronounced in the *Flex/Relax* task. Within JI (Fig. 3.3C), we observed a main effect of transition type ($F_{(3,216)} = 14.303$, $p < 0.0005$) and an interaction effect of group by type ($F_{(3,216)} = 8.978$, $p < 0.0005$). For the NI group, relaxation transitions were smoother than transitions made to capture cued torques in both tasks ($T_8 = 4.917$; $p = 0.001$). For SP participants, only the *Extend/Relax* task tended to exhibit relaxations that were smoother than torque target capture transitions; relaxations in the Flex/Relax task had *JI* values as large or larger than those in torque target capture transitions (Fig 3.3C). Thus, for SP participants, deficits of performance during the torque transition period appear to be more prevalent in the Flex/Relax task.

For both groups, target capture error tended to be lower when participants attempted to relax to baseline than when generating cued torques ($T_{22} = 2.758$, $p = 0.012$, Fig. 3.3D). Despite the appearance of elevated target capture errors at the end of E_R

transitions in the SP group, the interaction between group and transition type for $|\varepsilon_{end}|$ ($F_{(3,216)} = 2.921$, $p = 0.035$) did not remain significant after Bonferroni correction.

SP demonstrated greater hold variability when sustaining targeted torques than did NI, though both groups demonstrated less torque variability when relaxing than when generating a moderate torque. For the final behavioral measure, σ_{hold}, we again saw main effects of both trial type ($F_{(3,215)} = 69.467$, $p < 0.0005$) and an interaction effect of group by trial type ($F_{(3,215)} = 4.165$, $p = 0.007$, Fig. 3.3E). As expected, NI participants produced less torque variability when they were instructed to relax the arm than when they were to produce a steady-state elbow torque, regardless of task ($T_8 = 10.997$; $p < 0.0005$). While that same pattern was also observed in the SP group ($T_{12} = 5.683$; $p < 0.0005$), SP participants also appeared to exhibit task-dependent weakness in the pattern of σ_{hold} values, in that hold variability after torque target capture in the *Extend/Relax* task exceeded that in the Flex/Relax task ($T_{12} = 3.645$; $p = 0.003$) (Fig 3.3E).

Taken together, the results of these analyses found no systematic effect of elbow position, despite apparent deficits in the ability to produce and hold targeted torques (e.g., weakness), as well as deficits in the ability to relax the muscles about the elbow after active torque production (Fig 3.3A). Moreover, deficits of performance during the torque transition period appear to be more prevalent in the *Flex/Relax* task, whereas deficits of maintaining steady torque values are particularly prevalent in the *Extend/Relax* task.

Supplemental task performance

We next sought to test whether decreased torque production rates observed in the SP group during the primary experimental tasks reflected maximal performance in the SP

group or whether the reduced rates reflected task-specific constraints. We asked participants to perform a supplemental *Flex/Extend* task. This task required alternating transitions between elbow flexion and extension torques without intervening relaxation periods.

In the *Flex/Extend* task, both NI and SP participants increased their torque transition rate, and SP participants demonstrated the capacity to achieve peak rates of torque production similar to those produced by NI participants in the primary experimental tasks (Fig 3.4). NI participants nearly doubled their peak rates of flexion and extension torque production relative to the tasks involving rest ($F_E > F_R$: $T_8 = 10.140$, $p < 0.0005$; $E_F > E_R$: $T_8 = 9.620$, $p < 0.0005$). SP participants also increased their peak rates of flexion and extension torque production relative to the tasks involving rest ($F_E > F_R$: $T_{12} = 5.308$, $p < 0.0005$; $E_F > E_R$: $T_{12} = 3.316$, $p = 0.006$). Importantly, SP participants were able to produce peak rates of flexion and extension torque change in the *Flex/Extend* task that equaled or exceeded those produced by the NI participants in the *Flex/Relax* and *Extend/Relax* tasks (NI F_R = SP F_E: $T_{20} = 0.109$, $p=0.914$; NI E_R = SP E_F: $T_{20} = 0.184$, $p = 0.856$). Thus, limitations of maximal transition rate in the generate/relax tasks reflect task-specific constraints rather than maximal possible performance.

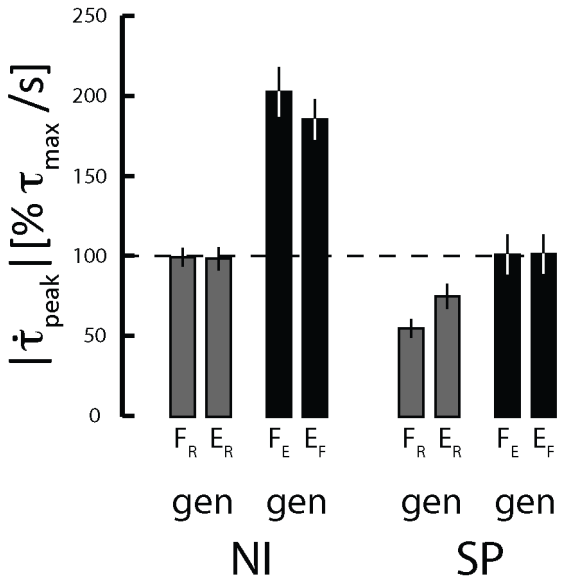

Figure 3.4: Peak rate of torque change during torque generation in primary (gray bars; flex from relax, extend from relax) and secondary (black bars; flex from extend, extend from flex) tasks. Error bars denote ± 1 S.E.M.

Coordination of agonist/antagonist muscle activation/deactivation during isometric elbow torque production/relaxation

We next quantified the impact of stroke on coordinating the amount of activation in elbow flexor/extensor muscle pairs during isometric elbow torque production and relaxation. We focused our analyses on three time windows: baseline activity when resting prior to the generation of either flexion or extension torques, during transitions into and out of cued torque generation, and during the maintenance of steady cued torque after transition.

Baseline (relaxed) EMGs prior to torque target capture:

When relaxing prior to torque generation, SP had elevated activity in the flexors and extensors relative to NI. To examine "resting" activity in the elbow flexor and extensor, we evaluated normalized baseline EMG values measured at least 2 seconds

after the most recent torque generation cue (i.e., at least 2 seconds into cued “relaxation” prior to the next torque generation). Repeated measures ANOVA applied to baseline EMG values for the primary flexor muscle revealed a main effect of participant group ($F_{(1,98)} = 771.429$, $p < 0.0005$) and transition type (F_R, E_R ; $F_{(1,98)} = 5.459$, $p = 0.022$), but no main effect of joint position, or interaction between factors (Fig 3.5A). Similarly, EMG values for the primary extensor muscle exhibited main effects of participant group ($F_{(1,95)} = 420.525$, $p < 0.0005$) and transition type (F_R, E_R ; $F_{(1,95)} = 11.739$, $p = 0.001$), but no main effect of joint position or interaction between factors (Fig 3.5B).

The group effect was driven by the inability of the stroke survivors to turn off, at "rest," EMG activities not only in the muscle primarily involved in the task (i.e., the primary flexor in the *Flex/Relax* task and the extensor in the *Extend/Relax* task), but also, to a lesser extent, in the selected antagonist muscle. The main effect of transition type appears to be driven predominantly by the SP group retaining larger quantities of activation in the task-related agonist muscle, i.e., there was more residual flexor activation when resting prior to torque generation during the Flex/Relax task and more residual extensor activation prior to extensor torque generation.

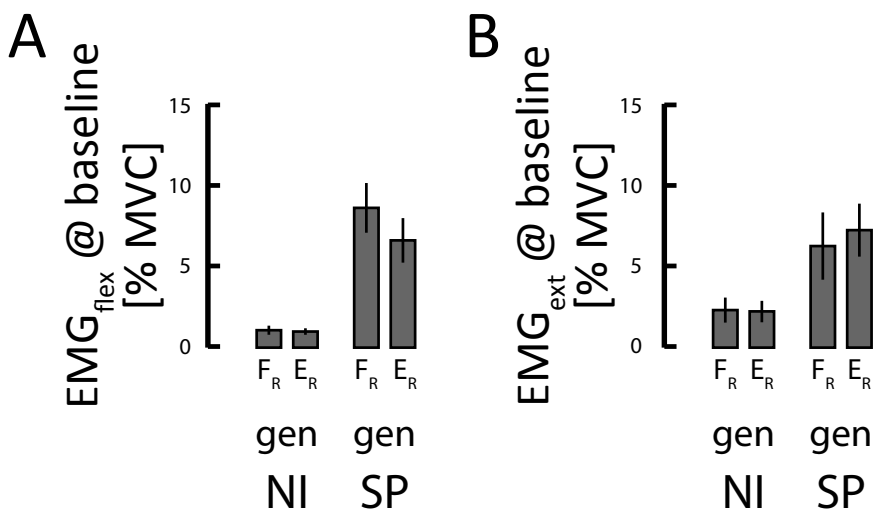

Figure 3.5: Muscle activity at resting baseline prior to torque production transition (Flex from relax, Extend from relax). Error bars indicate ± 1 S.E.M. A: Resting flexor activity in NI and SP (% MVIC). B: Resting extensor activity in NI and SP (% MVIC).

EMGs during and after torque target capture:

Both NI and SP were able to modulate activity in the flexors and extensors to generate torque, which is consistent with both groups' ability to generate isometric flexion and extension torques. We computed the difference between flexor EMGs in the time window just prior to $\dot{\tau}_{peak}$ vs. the baseline time window for transitions requiring torque production (ΔEMG_{flex}; Fig 3.6A), and a similar measure for extensor EMGs (ΔEMG_{ext}; Fig 3.6B). ANOVA applied to these two performance measures revealed main effects of transition type ($F_{(1,95)} > 127.993$, $p < 0.0005$, both cases), demonstrating a clear ability of both participant groups to modulate the primary flexors and extensors above and beyond the level of activation generated during "relaxed" baseline. We observed no main effect of participant group, limb position or interaction between factors.

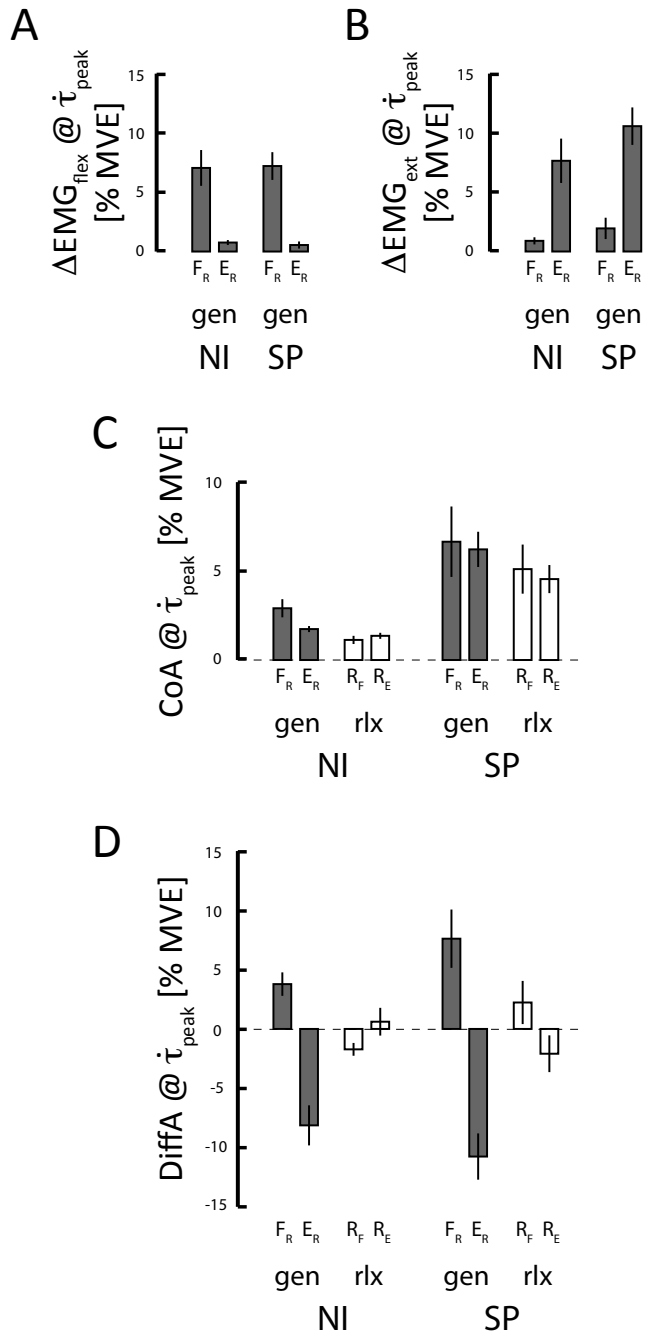

Figure 3.6: Modulation of muscle activity and coordination during torque initiation and cessation in NI and SP. Gray bars indicate torque production (Flex from relax, Extend from relax), white bars indicated torque cessation (Relax from flex, Relax from extend). Error bars indicate ± 1 S.E.M. All values are % MVE. A: Flexor activity, change from baseline to time of peak rate of change of torque. B: Extensor activity, change from baseline to time of peak rate of change of torque. C: Co-activation immediately prior to peak rate of change of torque in activation and cessation. D: Difference activation immediately prior to peak rate of change of torque in activation and cessation.

We found no evidence for a main effect of arm position or interaction between position and any factor in our analyses of EMG during goal-directed torque target capture.

Group analysis of the two EMG variables sensitive to flexor/extensor muscle coordination (muscle co-activation, CoA, and difference activation, DiffA) revealed systematic deficits of muscular coordination after stroke that were primarily related to an inability to "quiet" activity in agonists and antagonists. Compared with the NI group, the SP group had greater flexor/extensor co-activation (CoA) during all transition types; although both groups had greater CoA when generating torque than when relaxing (Fig. 3.6C). We found a main effect of group on CoA values during transition ($F_{(1,213)} = 536.686$, $p < 0.0005$). This effect was driven by the SP group producing more CoA than the NI group. We also found a main effect of transition type ($F_{(3,213)} = 36.136$, $p < 0.0005$) in that for both groups, we observed greater values of CoA during torque generation than during relaxations. Finally, we observed a significant interaction between group and transition type ($F_{(3,213)} = 10.929$, $p < 0.0005$). For CoA, the interaction appears to be driven by the presence of relatively larger CoA values during torque production in the E_R case vs. the F_R case in the NI group, but no such differences for the SP group.

Compared with NI, SP have greater DiffA in the agonist muscle during torque generation, and SP also maintain greater levels of agonist DiffA when relaxing from torque generation than do NI (Fig. 3.6D). We found a main effect of group on DiffA values during transition ($F_{(1,213)} = 5.158$, $p = 0.024$), as well as a main effect of transition type ($F_{(3,213)} = 115.745$, $p < 0.0005$). For both groups, both measures of coordination yielded greater values during torque generation than during relaxations. We also observed

a significant interaction between group and transition type for both coordination measures ($F_{(3,213)} = 10.935$, $p < 0.0005$). For DiffA the interaction appears to be driven primarily by differences during the relaxation conditions (e.g., compare NI $R_F < 0$ vs. SP $R_F \approx 0$), whereby NI participants appear to have relaxed the primary task-agonist muscle, or even actively engaged the extensor (task-antagonist muscle) to some degree during the R_F condition, whereas the SP maintained small amounts of net activation in the task-agonist muscle.

In summary, CoA values during transition in the SP group appear to reflect the elevated tonic activities observed during baseline, elevated relative to the NI group. DiffA values in the SP group appear almost normal when creating torques (i.e., quite like those produced by NI participants), and slightly elevated relative to the NI group when instructed to relax back to baseline, resting torque.

A similar pattern was obtained when we analyzed flexor/extensor muscle coordination during a time period after transition wherein participants were to maintain steady elbow torque values either at 20% of τ_{max} or at rest (Fig 3.7). For CoA, we again found main effects of participant group ($F_{(1,213)} = 715.495$, $p < 0.0005$) and a main effect of transition type ($F_{(3,213)} = 68284$, $p < 0.0005$), with both effects mirroring those observed during torque transition (i.e., Figs 3.6C). We also observed a significant interaction between group and transition type ($F_{(3,213)} = 15.876$, $p < 0.0005$).

Here, closer examination of SP data indicated that for those participants, there was no difference in CoA after transition when generating or relaxing from flexion ($F_R = R_F$; $T_{(12)} = 2.047$, $p = 0.063$), but there was greater CoA observed after transition in the extension torque generation task versus extension torque relaxation ($E_R > R_E$; $T_{(12)} =$

3.540, p = 0.004). Analysis of DiffA after transition yielded a pattern of results virtually identical to those described during transition. Once again, we found no evidence in support of a main effect of arm position, or interaction between position and any other factor in the analyses of EMG after target capture.

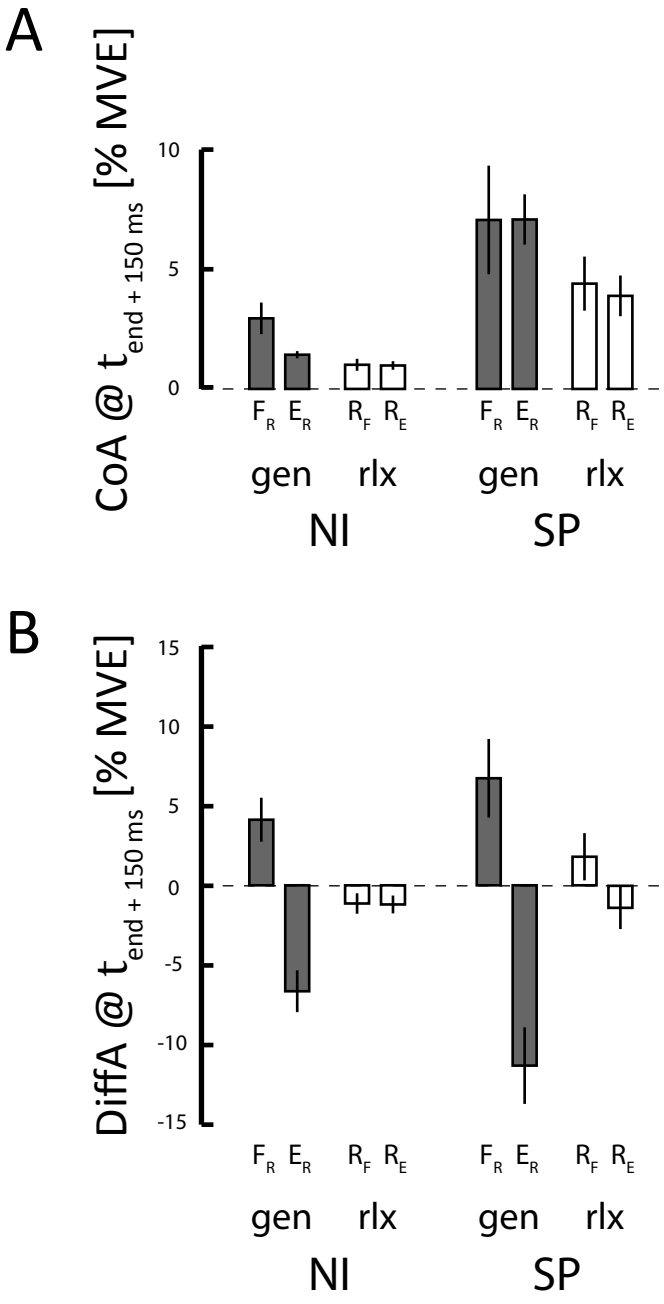

Figure 3.7: Muscle coordination during steady state torque production (gray bars; Flex from relax, Extend from relax) and relaxation (white bars, Relax from flex, Relax from extend). Error bars indicate ± 1 S.E.M. All values in units of % MVE A. Co-activity during torque production and relaxation. B. Difference activity during torque production and relaxation. Positive values indicate flexor more active than extensor, negative values indicate extensor more active than flexor. Dots (right) indicate mean values for individual participants.

Neuromuscular coordination: correlations between EMG and Torque measures

We used correlation and regression analysis to satisfy our study's first objective to quantify the extent to which deficits in agonist/antagonist muscle coordination degraded the ability to produce controlled, goal-directed changes in elbow joint torque after stroke. Because no main or interaction effects of arm position were found for the behavioral or EMG data, these analyses were performed with data from each SP participant averaged separately within each transition type. To limit the number of comparisons, we selected $|\dot{\tau}_{peak}|$ as our "during transition" dependent variable of interest, and σ_{hold} as our "after transition" dependent variable. We justify this choice because within the SP group, $|\dot{\tau}_{peak}|$ values were highly correlated with *ET* and *JI* values (*r = -0.676, and r* = -0.492, respectively; $p \leq 0.011$ and $n = 26$ in both cases) and because σ_{hold} and $|\varepsilon_{end}|$ were also highly correlated ($r = 0.813$, $p < 0.0005$, $n = 26$). We then selected four EMG variables that we thought might influence torque target capture performance during and after transitions. These variables included: CoA and DiffA values during transition, as well as CoA and DiffA values after transition.

Correlation analysis of the selected performance variables for torque initiation/termination and maintenance ($|\dot{\tau}_{peak}|$and σ_{hold}) revealed that stroke-related deficits in flexor/extensor muscle coordination correlate significantly to maintaining a steady level of targeted torque, but not to the maximal speed of transition. We found σ_{hold} correlated with CoA during and after transition in the F_R and R_F tasks ($|r| \geq 0.677$, $p \leq 0.010$, $n = 13$), and DiffA during and after transition in the E_R task ($|r| \geq 0.703$, $p \leq 0.007$, $n = 13$).

We next performed a regression analysis to distinguish the relative importance of specific sensory, physical, and cognitive impairments and muscle coordination in generating and holding a specified level of target torque. A series of eight forward regressions (two per transition type, using only data from that transition type) were used to identify relationships between our primary task performance variables $\left|\dot{\tau}_{peak}\right|$ and σ_{hold} and specific clinical impairment measures {FM_{LT}, MAS, MoCA, AMDT, τ_{max}} and muscle coordination measures {CoA during and after transition, DiffA during and after transition}. To preserve a sense of causality in this analysis, only EMG measures that occurred prior to the behavioral event were taken into consideration, so CoA and DiffA after transition were only used as independent variables in the regression model for σ_{hold}.

In our correlation analysis of our primary task performance variables ($\left|\dot{\tau}_{peak}\right|$and σ_{hold}) with measures of impairment and coordination, the only impairment or coordination variable that was found to be significantly correlated to $\left|\dot{\tau}_{peak}\right|$ was τ_{max} ($F_{(1,11)} = 5.597$, $p = 0.037$, adjusted $R^2 = 0.277$). DiffA during transition, CoA after transition, and AMDT were found to relate to σ_{hold} ($F_{(1,11)} \geq 10.196$, $p \leq 0.009$, adjusted $R^2 \geq 0.434$). Weakness impaired the ability to create rapid changes in torque production, while sensory impairment and impairments in coordination of agonist/antagonist muscle activation magnitude were associated with degraded ability to hold a consistent level of torque.

We performed a final pair of forward regression analyses to test our main hypothesis that deficits of agonist/antagonist coordination (as quantified by the selected task performance variables in each transition type) correlate significantly with global

measures of motor impairment (as quantified by FM_M scores) and deficits of motor function (as quantified by CAHAI scores). We also included the same set of impairment measures as potential variables in the model (e.g., τ_{max}, MAS, MoCA, FM_{LT}, and AMDT scores).

We used forward multiple regression to test the hypothesis that stroke-related deficits of agonist/antagonist coordination contribute significantly to motor impairment and deficits of motor function after stroke. Our models indicated that none of our coordination measures explained significant participant-by-participant variance in motor impairment scores, but a measure of flexor/extensor coordination was found to explain significant participant-by-participant variance in motor function scores, when combined with weakness and transition speed. When we treated FM_M score as the outcome variable of interest, we found only one impairment variable (weakness, i.e., τ_{max}) to be a significant contributor to this composite clinical measure of motor impairment [$F_{(2,23)}$ = 8.367, p = 0.015]. Weakness alone accounted for 38% of the variance in the dataset (adjusted r^2); none of the coordination measures – either alone or in combination - were found to correlate significantly with performance on the FM_M assessment. By contrast, three of the nine potential variables explained a significant amount of variance in the CAHAI scores [77% variance accounted for; $F_{(3,9)}$ = 14.956, p = 0.001]. These included weakness (τ_{max}), the maximal transition rate when relaxing from extension torque production ($\left|\dot{\tau}_{peak}\right|$), as well as a measure of coordination: DiffA after target acquisition when relaxing from extension torque production.

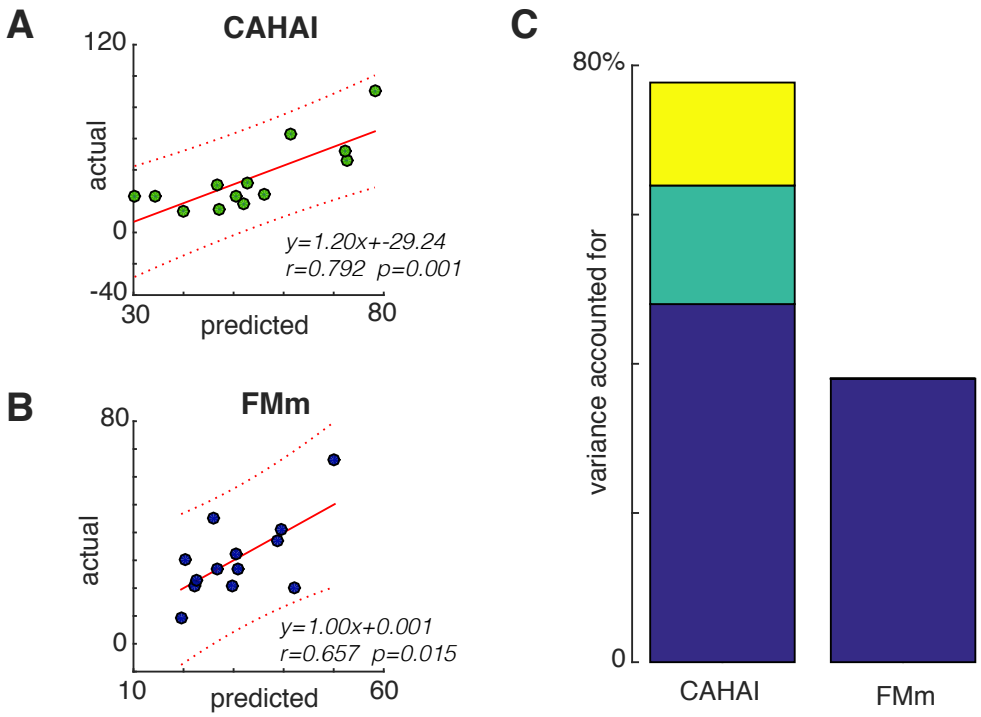

Figure 3.8: Results from forward regression analysis relating performance and EMG measures to impairment and function. A: Predicted and actual CAHAI values, solid line indicates line of best fit, dashed lines indicate 95% confidence interval; B: Predicted and actual FM_M values, red lines as in A; C: Percent variance accounted for by each model term, dark blue indicates τ_{max} , green indicates peak rate of change of torque when relaxing from extension, and yellow indicates after-transition DiffA when relaxing from extension.

Discussion

Consistent with common clinical observations of motor control deficits after stroke, stroke survivors exhibited impaired performance of a task that required goal-directed transitions between the generation of, and relaxation from, isometric, elbow flexion/extension torques. Transitions were slower, less smooth, less accurate, and more variable during the hold interval than those performed by neurologically-intact control participants. Within the cohort of stroke survivors, we found no compelling evidence that elbow joint configuration systematically impacted task performance (thus addressing our first experimental objective); if position-dependent effects were present, they must have

been small relative to the overall impact of stroke. Stroke-related deficits of task performance did not reflect hard neuromuscular constraints because the stroke survivors were able to increase rates of torque production in a secondary experimental task that required direct transitions between the production of flexion and extension torques. Instead, Stroke-related deficits in task performance reflected deficits in the strength and coordination of elbow flexor/extensor muscle activations; importantly, stroke survivors exhibited elevated activity in flexors and extensors throughout the entire task cycle (i.e., both when attempting to produce torques as well as when attempting to relax from torque production) despite the apparent ability to differentially activate flexor and extensor activities to a similar extent as NI control participants. Analyses addressing our second experimental objective found that within our cohort of stroke survivors, only a measure of elbow joint weakness (but no measures of task performance) accounted for participant-by-participant variations in Fugl-Meyer scores of motor impairment in the more-impacted arm. By contrast, weakness, speed of torque production, and measures of coordination between elbow flexor and extensor muscles all could account for significant portions of participant-by-participant variability in the Chedoke Arm and Hand Activities Inventory scores of motor function. These results support the conclusion that while motor impairment is influenced most strongly by weakness, deficits in the ability to coordinate flexor and extensor muscles at the elbow also contribute significantly to deficits of motor function after stroke.

In nearly all of the performance measures examined, we observed an interaction between participant group and torque transition type. NI participant performance during and after torque target capture exhibited variations primarily dependent on whether they

were actively producing torque or whether they were relaxing after producing a targeted torque. By contrast, SP participants exhibited performance variations that depended strongly on whether the task required production and relaxation of flexion torques vs. extension torques. For the SP group, performance deficits during transition were greater in the *Flex/Relax* task than the *Extend/Relax* task, and performance deficits during the hold period at the end of transition were greater in the *Extend/Relax* task than the *Flex/Relax* task. We found no significant evidence of position-dependent coordination in this study. Rather, SP participants exhibited inability to deactivate elbow flexor and extensor muscles across all limb configurations during both of the primary experimental tasks (consistent with the presence of hypertonia and reflecting a significant deficit of flexor/extensor coordination). While the SP group retained the ability to increase muscle activity above the tonic level of activity in both the primary flexors and extensors, they also varied considerably in their ability to coordinate activity between the flexors and extensors.

In the SP group, the ability to quickly modulate torque, $\left|\dot{\tau}_{peak}\right|$, was found to correlate significantly with weakness, while degraded ability to maintain a targeted level of torque, σ_{hold}, was found to correlate significantly with sensory impairments and deficits of agonist/antagonist muscle coordination. In the multivariate regression models used to quantify the relationship between specific impairments, performance variables, and agonist/antagonist muscle coordination, only weakness was found to significantly correlate with impairment (FM_M). Function (CAHAI) was found to be significantly correlated to weakness, ability to transition torques quickly, and ability to selectively activate muscles. Taken together, the results support the conclusion that deficits of

agonist/antagonist muscle coordination related to the inability to deactivate elbow flexor and extensor muscles contribute significantly to deficits of motor function after stroke, above and beyond the effect of muscle weakness.

Factors contributing to apparent weakness after stroke

It is well accepted – both in the clinic and in the literature - that weakness is a primary factor contributing to stroke-related deficits of motor control (Kamper et al. 2006, Lang et al. 2013, Trombly 1992, among others) and of motor function (Ada et al. 2006, Wagner et al. 2013, for a review see Lang et al. 2013). However, weakness is a composite measure with many potential etiologies, including muscular remodeling, motor unit changes, and changes in descending drive.

After stroke, perhaps the most immediate and apparent cause of weakness is disuse and the associated atrophy of muscle in the more-involved limb (Hafer-Macko et al. 2008). The structural properties of skeletal muscle are largely determined by function (Lieber 2002). Therefore, changes in use – regardless of cause – result in changes in muscle. While different muscle fiber types are known to have different force production characteristics, changes in muscle fiber type after stroke are not consistent. Some studies have found that muscle fibers change to predominantly fast fibers (DeDeyne et al. 2004, Jakobsson et al. 1991, Landin et al. 1997, Severinsen et al. 2016) which have high force capacity but also fatigue quickly, while others have found that muscle fibers in the more-involved limb become predominantly slow (Frontera et al. 1997), which would have lower force capacity and be more fatigue resistant.

Given the inconsistencies in changes in muscle fiber types, it is possible that decreased physiological cross-sectional area (PCSA) of more-impacted muscles is more important than changes in fiber type in decreased capacity for force generation after stroke. PCSA is a theoretical measure of the cumulative cross-sectional area of every fiber in a muscle, and it is correlated with a muscle's capacity to produce force (Lieber 2002). PCSA decreases as anatomical cross-sectional area of muscle decreases. After stroke, the anatomical cross-sectional area of more-impacted muscles decreases (Berenpas et al. 2016, English et al. 2010, Hunnicut and Gregory 2017, Ryan et al. 2002). Much of this decrease may be explained by a loss of contractile tissue. Western blot analysis of the quantity of myosin heavy chains (an indicator of contractile elements in muscle) in biopsies taken from muscles in the more- and less-involved limbs in SP showed significant decreases in all types of myosin heavy chains in the more-involved muscles (Hafer-Macko et al. 2008). Thus, loss of contractile tissue and the associated loss of muscle cross-sectional area contribute to decreased capacity for force production after stroke.

Additionally, torque measured about a joint (a logical measure of strength/weakness) is the net of all muscle torques applied about that joint. Thus, increased force generated by the task-agonist muscle would increase the measured force, while increased force generated by the task-antagonist muscle would decrease the measured force and contribute to observed weakness.

After stroke, there is frequently increased passive tension in antagonist muscles (Eby et al. 2016, Frieden and Lieber 2003). Mechanical causes of passive tension include shortening of the muscle through deletion of sarcomeres (Ada et al. 2006, Gao and Zhang

2008) and increases in connective tissue that is resistant to stretch (Booth et al. 2001, Lieber 2002). Therefore, increased passive tension in muscles can lead to to measured weakness after stroke.

Additionally, changes in motor units after stroke may contribute to observed weakness. Skeletal muscle contracts – and therefore exerts force – when it is activated by motor units (Lieber 2002). Stroke has been associated with changes in motor units innervating the paretic muscles, including a reduction in the number of motor units (Li et al. 2011), disordered recruitment of motor units (Hu et al. 2012), and abnormal saturation of firing rates within individual motor units. In spastic muscle, which is common after stroke, these patterns are observed even when the overall descending command is increasing (Gemperline et al. 1995, Mottram et al. 2014, cf. McCrea et al. 2005).

Many of these changes may be related to changes in descending control after stroke. The middle cerebral artery supplies many areas known to be components of the corticospinal motor tract (CS; Lundy-Eckman 2007), and it is also the most frequent site of stroke (Bogousslavsky et al. 1988), thus the CS tract is often damaged after stroke. Controlled lesion studies in non-human primates suggest that lost CS input is replaced by input from the reticulospinal tract (RS; Baker 2011, Zaaimi et al. 2012). Compared with the CS tract, the RS tract makes weak, diffuse connections to motor units (Baker 2011, Matsuyama et al. 1997, Peterson et al. 1975, Riddle et al. 2009). Additionally, the CS tract primarily uses glutamate as its excitatory neurotransmitter (Al Masri 2011), while the RS tract uses monoamines which are much slower – both in activation and in deactivation – than glutamate (Lundy-Eckman 2007). Finally, loss of CS input can lead

to changes in spinal circuits giving rise to altered α-motor neuron excitability (Mazevet et al. 2003) and reflex patterns (Dewald et al. 1999).

These changes in descending drive can contribute to weakness by causing decreased activation of motor units and adverse changes in inter-muscular coordination between muscles about a single joint. Maximal net joint torque will be reduced if the task-agonist muscle cannot be fully activated due to weak descending drive. The RS tract can only drive approximately 20% of the motor unit activation generated by CS and may therefore cause decreased activation of task-agonist muscle (Riddle et al. 2009). Maximal net joint torque will also be reduced if task-antagonists spanning a joint work against the task-agonist muscles (Levin et al. 2000). Consistent with the diffuse projections of RS, this can result from inability to selectively activate individual muscles (Lang and Scheiber 2004).

Another form of inter-muscular dis-coordination can arise from deficits in timing muscle activation and deactivation of individual muscles spanning the joints (cf. Cirstea et al. 2003). These deficits are consistent with the slower activation and inactivation time course of monoamine neurotransmitters of RS compared with the glutamatergic drive from CS (Lundy-Eckman 2007). For example, delays in the initiation (cf. Canning et al. 1999) and termination (Chae et al. 2002, Kautz and Brown 1998, McCrea et al. 2003) of motor neuron activity will compromise performance in most tasks requiring torque production (cf. Canning et al. 2000).

The results of the current study supply independent confirmation of the significance of weakness after stroke by demonstrating that τ_{max} correlated positively both with FM_M scores and CAHAI scores. Although deficits of τ_{max} in the SP group

relative to NI participants could have been due to any of the factors enumerated above – either alone or in combination – it is likely that deficits of inter-muscular coordination played an important contributing role in our study. Indeed, a novelty of our study is that when we identified a model for motor function (CAHAI scores), significant contributions were ascribed to weakness, rate of torque generation, and a measure of flexor/extensor coordination (the value of DiffA) obtained during the hold period immediately after isometric torque target capture.

Further insight into this result can be drawn from the correlation analyses that characterized how deficits in agonist/antagonist muscle coordination degraded the ability to produce controlled, goal-directed elbow joint torques (our first study objective). Even though differences in resting baseline EMG values between the NI and SP groups averaged only ~4 to 5% of their respective MVIC values (Figs 3.6A and 3.6B), the inability to suppress the primary muscle activities when nominally at rest appears to be a key deficit of neuromotor control after stroke; participants who produced greater levels of CoA during and after transition yielded worse hold performances (higher σ_{hold} values) in both primary tasks. Conversely, stroke survivors who could generate greater DiffA values produced better hold performance (lower σ_{hold} values). These results demonstrate that the ability to selectively activate elbow flexor and extensor muscles - independent of weakness - is important for producing well-controlled submaximal elbow joint torques. Because DiffA after target capture also was found to be significantly related to CAHAI scores, we conclude that inability to selectively activate elbow flexor and extensor muscles during the maintenance of steady elbow torques contributes importantly to deficits of motor function after stroke.

Potential mechanisms of disordered agonist/antagonist coordination

In order to produce task-directed movement, the task-agonist and task-antagonist muscles must be selectively activated and deactivated to produce the necessary forces for movement. These patterns of activation and deactivation need to be coordinated both in time and in magnitude. After stroke, the ability to selectively activate muscle is often impaired (Lang et al. 2004, Lang et al. 2013). In the descending RS pathway, a single axon can project across multiple spinal roots (Peterson et al. 1975), thus innervating motoneuron pools associated with multiple muscles – potentially spread across multiple limbs – from a single descending axon. Axons originating in the CS, however, tend to be focused in their innervation on a small number of functionally-linked motoneuron pools (Buys et al. 1986). Thus, ability to selectively activate muscle is decreased after damage to the CS tract. Additionally, loss of targeted descending inhibition from CS can impair the ability to selectively deactivate muscle after stroke (Lundberg and Voorhoeve 1962).

The timing of activation and deactivation may be impaired due to characteristics of the RS tract. RS excitation of motoneurons is approximately 80% weaker than similar input from CS (Riddle et al. 2009), so more excitatory input from RS would be required to drive a motoneuron to threshold than if driven by CS. Additionally, monoamines released by RS are slower to act and linger much longer in the synapse than does glutamate released by CS. Since monoamine transmitters are slower to degrade than glutamate, and can persist for minutes to hours after release (Lundy-Eckman 2007), this could lead to motoneurons remaining closer to threshold after excitation unless they receive sufficient inhibitory input.

Damage to CS can reduce descending inhibition (Lundberg and Voorhoeve 1962), which combined with lingering excitatory effects of monoamines could lead to persistent muscle activation. The incidence and consequence of increased background muscle activity has been studied using surface EMG (Burne et al. 2005) and intramuscular EMG (iEMG) (Mottam et al. 2009; Mottram et al. 2010; Chang et al. 2013). Each of these studies describes the presence of elevated EMG activity from spastic muscles that were nominally at rest. Burne and colleagues (2005) examined mechanical responses to imposed elbow perturbations in NI and hemiparetic arms of participants with stroke. This study found that the most conspicuous difference between the groups aside from weakness, was a modest rise (~3% of normal MVIC) in the background levels of contraction when the hemiparetic limbs were at rest. This is similar to the level of tonic activity observed at rest (baseline) in the current study (cf., Figs 3.5A and 3.5B).

The consequence of this elevated tonic activity was that when the hemiparetic limbs were mechanically perturbed, the stretch reflex and the passive joint resistance were increased relative to resting normal arms (Burne et al. 2005). Importantly, when normal limbs voluntarily generated a similar amount of background flexor EMG activity, reflex gain and joint mechanical resistance were comparable across the two participant groups (Burne et al. 2005). Burne and colleagues concluded: "the rise in resting background muscle activity is a primary factor in the greater prominence of spastic signs (viz., increased reflex gain and passive joint resistance)."

Weakness and impaired neuromuscular coordination may also contribute to slowness

Impairments in force production capacity of muscle and in neuromuscular coordination after stroke may also contribute to slowness observed in the SP group. First, aforementioned changes in descending control may lead to slowness due to decreased rate of muscle activation. Weaker (Baker 2011), less organized (Matsuyama et al. 1997, Peterson et al. 1975, Riddle et al. 2009) descending drive using slow neurotransmitters (Lundy-Eckman 2007) would logically lead to slower contraction of individual muscles. Additionally, if antagonist muscles are generating forces – passively or actively – those forces must be overcome by the agonist muscles in order to create a net torque about the joint in the desired direction. Muscle can produce greater force when contracting slowly than when contracting quickly (Lieber 2002). Given that force generation capacity tends to be degraded after stroke, and greater levels of opposing force may be applied to a joint, slowness may be an adaptive strategy to allow weakened muscle to overcome increased force.

Clinical implications

Our current observations suggest that deficits of motor function after stroke are due, not only to weakness, but also to deficits in the ability overcome spontaneous activity within elbow flexor and extensor muscles. To enable clinicians to address the stroke-related deficits of sensorimotor control that most significantly compromise motor function, it will be important to develop therapeutic interventions that are able to reduce low-levels of sustained activity in spastic muscles at rest, while also promoting the

recovery of strength and reciprocal agonist/antagonist coordination required for complete independence in the performance of everyday activities.

Most current therapeutic approaches do not appear to address this specific ideal. Although aerobic and strength training may be able to improve general fitness while addressing certain aspects of weakness due to muscle remodeling (Hafer-Macko et al. 2008), that approach is less effective than task-specific training for improving coordination during tasks such as goal-directed reaching, especially in lower-functioning individuals (Thielman et al. 2004). Stretching and re-positioning joints in their full range may be effective at preventing contracture (Ada et al. 2001; see also Stoeckmann 2001), but this approach does little to improve strength and/or coordination, and may actually impede the patient's ability to terminate activation within the stretched spastic muscle. (c.f., Seo et al. 2009).

Contemporary implementations of high-intensity motor training protocols such as constraint-induced movement therapy (Taub and Morris 2001) and rehabilitation robotic therapy (e.g., Lum et al. 2002; Reinkensmeyer et al. 2012) focus almost exclusively on task-specific training without directly addressing the root causes of strength and coordination deficits. Similarly, the use of certain pharmacological agents (c.f., Butefisch et al. 2002) and non-invasive brain stimulation techniques such as transcranial magnetic stimulation (c.f., Hoyer and Celnik 2011) and tDCS (Brown et al. 2003; but see also Levy et al. 2008) may enhance motor plasticity during recovery, they also do not directly address coordination deficits.

Stoeckmann and colleagues (2009) considered the effect of resistive load type on muscle recruitment and co-activation during reaching movements performed by the

more-impacted and less-impacted arm after stroke. In this study, participants performed in-line reaches against an elastic load, a viscous load, and a mass load in order to characterize the muscle agonist/antagonist coordination strategies that survivors of stroke would use against these different load types. Survivors of stroke presented with motor deficits in both arms, with the more-impacted arm having the same, elevated co-activation response to all three load types. In the less-impacted arm, however, elastic and viscous loads were associated with strong activation, and mass and viscous loads were associated with minimal co-contraction. This selective matching of resistive load type to specific coordination deficits (timing, torque production) warrants further investigation.

Additionally, there are several existing pharmaceutical treatments for managing abnormal muscle tone and spasticity (Olvey et al. 2010). Concurrent pharmaceutical intervention to manage muscle tone may improve muscle coordination to some extent (Pandyan et al. 2002). Targeted or general anti-spasmodic treatments may be useful for reducing the persistent levels of co-activation (elevated muscle tone) observed after volitional effort (c.f. Figs. 3.6C, 3.7A). We suggest that further studies focus on therapeutic approaches combining appropriate, physician-guided pharmaceutical treatment of muscle tone abnormalities with high-intensity therapies designed to train motor coordination.

Conclusion

The present study supports previous findings that coordination of muscle activation timing and activation magnitude in agonist/antagonist pairs is impaired after stroke. This discoordination was associated with impaired ability to quickly produce and

hold moderate torques, and to relax from torque creation. Additionally, our findings indicate that the ability to coordinate agonist/antagonist muscle pairs, in addition to weakness, is itself a significant factor contributing to loss of function after stroke.

CHAPTER 4: DIFFERENTIAL IMPAIRMENT OF STABILIZATION, MOVEMENT AFTER STROKE RELATED TO DEFICITS IN PROPRIOCEPTION

Many survivors of stroke experience persistent deficits in motor function that can negatively impact important activities of daily living. A key component for many common activities is moving the arm to bring the hand to an object. Even a simple behavior, like a point-to-point movement, consists of a series of stabilization and movement actions that allow the arm to perform a desired task. It has previously been reported that stroke can impact these stabilization and movement actions differentially. We sought to test the hypothesis that deficits in the control and coordination of arm stabilization and movement actions correlate significantly with deficits of motor function after stroke. Survivors of unilateral stroke and neurologically intact control participants attempted to perform six different tasks that combined two elementary behaviors in isolation and in sequential combination: elbow stabilization against perturbations, and flexion/extension movements of the elbow. We quantified performance on these tasks in order to determine the extent to which stroke-related impairments impact the kinematics and coordination of simple control actions contributing to moving the arm and holding it still. We then tested our hypothesis by examining the extent to which motor impairments and/or the ability to stabilize and move the arm can be used to model a common clinical assessment of motor function after stroke. For both participant groups (stroke survivors and neurologically intact controls), we found that sequential movement and stabilization actions interact in a manner consistent with the idea that stabilization and movement behaviors recruit distinct neuromuscular control actions. While we furthermore found that stroke-related deficits in proprioception degrade the ability to stabilize the arm, we

paradoxically found that stroke survivors with impaired proprioception produced smoother and more accurate movements than did stroke survivors with clinically intact proprioception. This finding supports the idea that proprioceptive feedback contributes differentially to the control of limb stabilization and movement. Contrary to our original hypothesis, we found that above and beyond the effects of weakness, none of the experimental measures of elbow control and coordination contributed significantly to a predictive model of motor function after stroke (as measured by the Chedoke Arm and Hand Activities Inventory).

Introduction

Stabilization and reaching behaviors performed with the arm contribute positively to quality of life because they facilitate interaction with, and manipulation of, objects in the environment. However, approximately half of stroke survivors live with chronic motor deficits that impact many tasks including the simplest of point-to-point reaching (Roger et al. 2012) and stabilization behaviors (Scheidt and Stoeckmann 2007). Movement-related deficits can include limitations in range of motion, muscle weakness, slow and segmented movement, as well as and inaccuracy and instability of hand position stabilization (Cirstea and Levin 2000, Kamper et al. 2002, Levin 1996, Roby-Brami et al. 1997, Scheidt and Stoeckmann 2007, Trombly 1992).

A single point-to-point movement has been proposed to be a ‘motor primitive,’ a pre-programmed behavior that is used as a building block for other, more complicated behaviors (Flash and Hogan 1985, Schaal and Atkeson 1998, Sheridan 1984). However, there is evidence to suggest that point-to-point movements are controlled by a series of

distinct neural mechanisms enacted sequentially (Flash and Hochner 2005, Humphrey and Reed 1983). An experiment performed by Sainburg and colleagues (1999) provides evidence that movement is initiated by a feedforward, proprioception-dependent movement controller, that errors in the initial movement trajectory are corrected using a feedback, vision-dependent controller, and that final endpoint stabilization is controlled by a positional stabilization controller that is agnostic of the dynamics of movement. In healthy point-to-point movements, these three control actions appear to be executed sequentially (Sainburg et al. 1999), with the control actions overlapping in time (thus blending the control phases into one another) to produce smooth and accurate point-to-point movements.

Later, Scheidt and Ghez (2007) examined closely the limb movement controller that is used to initiate movements and the limb position controller that is used to stabilize the limb pose at the end of movement. They accomplished this by testing two-joint planar movements using a paradigm of visuomotor adaptation in both point-to-point "reaching" movements (presumed to invoke a specific sequence of control actions: arm movement generation → limb position stabilization) and out-and-back reversal movements or "slicing" (presumed to invoke a different sequence of control actions: movement generation → movement generation → limb position stabilization). Their findings demonstrated that movement trajectory and final stabilized limb positions are influenced by separate, differentially adaptable neural control mechanisms. In support of this idea, Ghez and colleagues (2007) presented evidence that slice reversals and reach endpoints are represented in distinct reference frames, with slice reversals represented in a hand-

centered reference frame and reach endpoints represented in an ego-centric (i.e., eye-, head-, or shoulder-centered) reference frame.

The existence of separate movement and position controllers was further demonstrated by Scheidt and colleagues (2011), who studied participants who practiced performing a single-joint, point-to-point reaching task in which limb impedance at the end of the reach was altered by means of cued elbow flexor/extensor muscle co-activation. Analysis of electromyographic activity recorded during practiced reaches and occasional unpracticed reversal movements found that both the reaches and reversals were initiated using a common, shared control action that launched the hand from its starting position to an initial spatial goal. Both also shared a common limb-position stabilization controller that invoked similar levels of elevated co-contraction about their different, desired final positions. The kinematic consequence of this control policy was that whereas reaches performed in the presence of terminal co-contraction were highly accurate about the reach target, initial trajectories of unpracticed reversals far overshot that same spatial goal (Scheidt et al. 2011). This outcome was predicted by a model of movement control wherein the brain uses different mechanisms to plan the hand's initial trajectory and final position in point-to-point movements, that it implements these control actions sequentially, and that trajectory planning does not account for specific impedance values to be implemented about the final stabilized limb position.

Experimental evidence that the limb movement and position controllers can be affected differentially by stroke was provided by Scheidt and Stoeckmann (2007), who found that whereas all but the most impaired stroke survivors could make feedforward reaching movements in the presence of an unpredictable perturbation, nearly all stroke

survivors had marked deficits in their ability to bring the hand of their more-involved arm to rest at the target. Participants with impairments in proprioception had greater stabilization deficits (i.e., higher variability at the end of movement) than those with intact proprioception.

The objective of the current experiment was to investigate the extent to which stroke impairs the ability to control and coordinate positional and movement control actions in the arm, and to determine how deficits in coordination between these control actions correlate with deficits in motor function. Building on the work of Ghez and colleagues (Kalakanis et al., 1999, Scheidt and Ghez, 2007; Ghez et al., 2007), we operationally define movement control actions as those that give rise to feedforward, point-to-point movements, and we define positional control actions that engage neuromusculoskeletal feedback mechanisms to stabilize the limb about a desired position. We operationally define "coordination" between control actions as the influence exerted by one control action on prior or subsequent control actions.

We studied these basic control actions by requiring survivors of unilateral stroke and neurologically intact individuals to perform sequential combinations of targeted, single-joint point-to-point movements at the elbow, and forearm stabilizations against perturbation. We examined performance in the stabilization task in isolation and in sequential combination with cued movements both to examine the effect of somatosensory feedback deficits on the positional controller and to determine the impact of prior and subsequent movement on positional control. We examined performance in the initial feed-forward portion of targeted elbow point-to-point movements, in isolation and in sequential combination with prior stabilization actions, in order to evaluate the

extent to which the feedforward movement plan driven by the movement controller is influenced by deficits of somatosensory feedback, and by the performance of prior stabilizations. We then used clinical measures of impairment along with kinematic and electromyographic measures of movement and position control and coordination in a multilinear regression analysis to test the hypothesis that deficits in the control and coordination of arm stabilization and movement actions correlate significantly with deficits of motor function after stroke.

Methods

Participant characteristics and inclusion criteria:

Twenty-one adults provided written informed consent to participate in these experiments, which required participants to perform elbow stabilization and point-to-point movement tasks - in isolation and sequentially - in a single experimental session that lasted approximately two hours. All participants provided written informed consent in compliance with Marquette University Institutional Review Board protocols. Ten participants were survivors of stroke (SP; 62.1 ± 5.3 years (mean+/-SD); 4 F), and eleven participants were neurologically normal, age-range matched controls (NI; 59.8 ± 13 years; 4 F). All stroke participants were more than 6-months post-stroke, were able to follow two-step instructions (assessed during participant screening), and could perform the experiment task comfortably.

Stroke participants were excluded from participation if they could not lift the more-impacted arm within 20˚ of the horizontal plane (supported), experienced pain when lifting the more-impacted arm, if they had received botulinum toxin injections in

elbow flexors or extensors within 4 months prior to the experiment, or if they were diagnosed with any other condition or disease that is known to interfere with neuromuscular function. The presence of contracture in the arm or shoulder did not exclude stroke survivors from participating in the experiment unless it prevented them from performing the task comfortably. Medical records were solicited for all stroke participants to verify lesion location and type.

Clinical Assessments:

All stroke participants underwent a battery of clinical tests administered by a licensed physical therapist on a day prior to the reported experimental session (Table 4.1). We evaluated impairment in the upper extremity using the Fugl-Meyer Assessment of Sensorimotor Recovery After Stroke (FMA, Fugl-Meyer et al. 1975). The upper-extremity motor portion of the FMA (FM_M) is rated on a scale of 0 to 66 with a score of 0 indicating a complete lack of reflexes and volitional movement in the more-impacted arm whereas a score of 66 indicates intact reflexes, arm-, and grasp-movements. The upper extremity sensory portion of the FMA includes a coarse test of proprioceptive acuity (FM_P, the clinical "up or down?" test, DeGowin et al., 1987; Epstein et al., 2008) which was used to assess overall proprioceptive discrimination at the thumb, wrist, and elbow joints. Proprioception at each joint is graded "intact" (2), "impaired" (1), or "absent" (0). Scores were summed across joints to provide a total of 6 points possible for the FM_P. The upper extremity light touch portion of the FMA (FM_{LT}) was also assessed. In this test, the participant's ability to detect light touch on the more-impacted arm is judged to be "intact" (2), "impaired" (1), or "absent" (0), with a maximal score of 4 points for FM_{LT}.

An additional laboratory test of proprioceptive integrity (AMDT) was also administered. This measure has been described previously (Mrotek et al., 2017).

Additional assessments screened for strength, mild cognitive impairment, spasticity, and motor function in the more-impacted limb. Maximal average elbow torque production (τ_{max}) was measured while participants performed 6 isometric, maximal voluntary elbow flexion and extension exertions with a load cell at the elbow measuring torque. The maximal torque values were averaged to calculate a single measure of strength about the more-impacted elbow (see Chapter 3 for detailed methods). We screened for cognitive impairments using the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). The MoCA was designed to detect impairment of short-term memory recall, visuospatial information processing, executive function, attention, working memory, and language. MoCA scores ≥ 26 on a 30-point scale are considered normal whereas scores < 25 suggest cognitive impairment. Due to the verbal nature of many test responses, MoCA scores can be confounded by aphasia (participants with aphasia are noted in Table 4.1).

We tested muscle tone of the more-impacted elbow flexors and extensors using the Modified Ashworth Scale (MAS, Bohannon and Smith 1987). This scale grades flexor and extensor muscle tone about a joint on a scale of 0 to 4 where a score of 0 indicates that there is no increase in tone compared to the less-impacted side, and a score of 4 indicates muscle tone so severe as to render the tested joint rigid. MAS scores for more-impacted elbow flexors and extensors were averaged to obtain an overall estimate of muscle tone at the more-impacted elbow. We used the 13-item Chedoke Arm and Hand Activity Inventory (CAHAI; Gowland et al. 1993) to assess function in the more-

impacted limb during bimanual activities of daily living such as pouring a glass of water and buttoning a shirt. Individual assessments on the CAHAI score from 1 to 7, giving a maximum possible total of 91 points. An item score of 1 indicates that the participant could not perform the task whereas a score of 7 indicates that the more-impacted arm participated fully and efficiently in the bimanual task. Clinical assessment scores are reported in Table 4.1.

*Table 4.1: Participant characteristics. Grp: Group; ID: participant number; ‡: presence of expressive aphasia; M: Male; F: Female; Dom: Dominant hand; θ_{goal}: Distance of flex target from home in degrees; Flex: Selected flexor; BRD: Brachioradialis; BICS: Short head of biceps; BICL: Long head of biceps; Ext: Selected extensor; TRILT: lateral head of triceps; TRILG: long head of triceps; FM_M: Upper extremity motor portion of Fugl-Meyer Assessment; CAHAI: Chedoke Arm and Hand Activity Inventory; FM_P: Upper extremity sensory proprioception portion of Fugl-Meyer Assessment, summed at thumb, wrist, elbow; MoCA: Montreal Cognitive Assessment; I: Ischemic; H: Hemorrhagic; MCA: middle cerebral artery; BG: basal ganglia; PCA: posterior cerebral artery; * not applicable; ** information not available.*

Grp.	ID	Age	Sex	Test Hand	Dom. Hand	θ_{goal}	Flex.	Ext.	FM_M	CAHAI	FM_P	MAS EL.	MoCA	Years since stroke	Lesion Type	Lesion Location
NI	1	62	M	R	R	30°	BRD	TRILT	*	*	*	*	*	*	*	*
NI	2	62	F	R	R	30°	BRD	TRILT	*	*	*	*	*	*	*	*
NI	3	60	M	R	R	30°	BICS	TRILT	*	*	*	*	*	*	*	*
NI	4	63	F	R	R	30°	BRD	TRILT	*	*	*	*	*	*	*	*
NI	5	72	M	R	R	30°	BICS	TRILT	*	*	*	*	*	*	*	*
NI	6	66	F	R	R	30°	BICS	TRILT	*	*	*	*	*	*	*	*
NI	7	70	M	R	R	30°	BICS	TRILG	*	*	*	*	*	*	*	*
NI	8	76	M	R	R	30°	BRD	TRILT	*	*	*	*	*	*	*	*
NI	9	51	F	R	R	30°	BICS	TRILG	*	*	*	*	*	*	*	*
NI	10	49	M	R	R	30°	BICL	TRILT	*	*	*	*	*	*	*	*
NI	11	30	M	R	R	30°	BICS	TRILT	*	*	*	*	*	*	*	*
SP	101‡	57	M	L	R	16°	BICS	TRILG	27	18	1	1.5	27	12	I	R: Midbrain
SP	102‡	59	M	R	R	30°	BICS	TRILT	20	24	6	4	26†	7	I	L: MCA, BG, Insular Cortex
SP	104‡	52	M	R	R	21°	BICL	TRILT	21	23	6	3.5	23†	13	**	L: **
SP	106‡	64	F	R	R	30°	BRD	TRILG	45	32	2	2	14†	24	**	L: **
SP	107‡	61	M	R	R	21°	BICL	TRILG	27	15	1	2.5	10†	12	I	L: MCA Distribution
SP	110	62	M	L	R	30°	BRD	TRILG	41	63	6	4.5	23	7	I	R: BG & Caudate
SP	111‡	69	F	R	R	17°	BRD	TRILG	23	46	6	3	25	35	H	L: PCA
SP	113	63	F	L	R	30°	BICS	TRILT	37	52	3	3.5	22	10	**	R: **
SP	114	64	M	L	R	30°	BRD	TRILG	66	90	6	0	24	7	I	R: Multi-focus Periventricular White Matter
SP	115	70	F	L	L	30°	BICS	TRILT	32	30	6	1.5	22	13	H	R: **

Experimental setup:

Participants were positioned in a manner to isolate motion to flexion and extension of the elbow to the extent possible. Participants sat in an adjustable, high-backed chair with their forearm and hand (palm down) fixed to the handle of a single degree-of-freedom robot (Fig. 4.1A). The elbow was supported and aligned with the robot's rotational axis such that the participant's hand moved along an arc in the horizontal plane (Scheidt et al., 2011). The participant's torso was secured to the chair with a neoprene harness in order to prevent compensatory movements of the trunk (Roby-Brami et al. 2003, Cirstea and Levin 2000). The more-impacted (SP) or dominant (NI) arm was positioned such that the upper arm was abducted 0° to 15° below horizontal, and horizontally adducted/flexed 0° to 15°. SP were fitted with a wrist brace in order to prevent wrist flexion during the task.

The robotic device is powered by a low-inertia, brushless DC motor with an integrated resolver (D061A DC, Kollmorgen, Radford, VA), which can measure joint angle with a resolution better than 0.01°. The device is also outfitted with a 6 degree-of-freedom load cell (67M25A-I40-A-200N12; JR3, Woodland, CA), which measures forces and torques applied to the adjustable handle. All control operations and data sampling were performed at 1000 samples per second with 16-bit resolution, and the resulting data were stored to hard drive for off-line analysis.

An opaque screen obstructed the participant's view of the tested arm. Participants were instructed to direct their attention to a vertically-mounted computer monitor that was located 60 cm directly in front of them. The computer monitor (Fig. 4.1B) displayed visual cues and provided feedback related to task performance, as described below.

Surface electromyograms (EMG) were recorded from three elbow flexor muscles (short head of the biceps, BICS; long head of the biceps, BICL; and brachioradialis, BRD) and two elbow extensor muscles (lateral head of the triceps, TRILT; and long head of the triceps, TRILG). EMG signals were band-pass filtered with an active, 20-450 Hz anti-aliasing filter and amplified with a gain of 10,000 (DE-2.1 electrodes and Bagnoli 8 Amplifier; Delsys Inc., Taunton, MA) prior to digitization at a rate of 1000 samples per second.

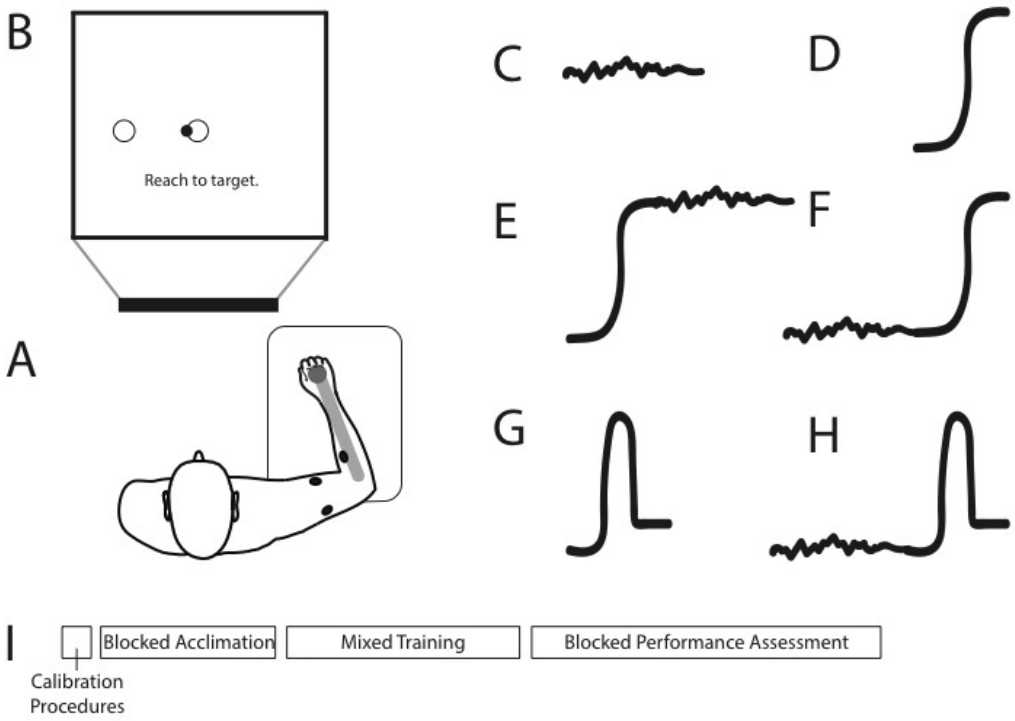

Figure 4.1: Experimental setup and tasks. A: Participant setup (opaque screen not shown); B: Participant viewed task instructions, target locations, and performance feedback on a visual display; C-H: Cartoon depictions trajectories of task types over time, C: Stabilize (S); D: Flex (FLX); E: Flex, Stabilize (FLX-S); F: Stabilize, Flex (S-FLX); G: Flex, Extend (REV); H: Stabilize, Flex, Extend (S-REV); I: Order of experiment blocks.

Experimental Procedures:

Each participant performed two calibration procedures. The first was designed to obtain data with which we could normalize each participant's EMG recordings for subsequent comparison across participants and groups. The second was designed to identify movement targets that were within each participant's active range of motion. For the first procedure, participants performed resting and maximal voluntary exertion

(MVE) tasks. Participants were seated in a high-backed chair away from the robot. The arm was supported against gravity and the elbow bent to approximately 90º flexion. Manual resistance was provided as each participant was instructed to "flex the elbow as hard as you can" for 10 seconds while EMG signals were recorded. The participant rested with the arm supported for 30 seconds and was then asked to "extend the elbow as hard as you can" for 10 seconds while EMG signals were recorded. After the two maximal exertions were recorded, the participant rested for at least 30 seconds, and was instructed to "relax the arm, let it become heavy" for 10 seconds to record resting EMG signals.

For the second procedure, participants familiarized themselves with the movement space by performing 5 to 7 elbow flexion trials to verify that they could move comfortably over an appropriate range of elbow joint angles for the upcoming tasks. A *home target* (θ_{home}) was placed at 90˚ of elbow flexion relative to full extension (see Fig. 4.1A); this position was within the range of comfort for all participants. For most participants, a default *goal target* (θ_{goal}) was located at an elbow joint angle that was 30˚ flexed relative to the home position (i.e., at 120° of elbow flexion). Target locations were adjusted for individual stroke survivors if they were unable to consistently flex the elbow to the default goal target (see Table 4.1 for participant-specific target locations). A *return target* (θ_{return}) was located at an elbow joint angle that was 3˚ flexed relative to the home position (i.e., at 93° of elbow flexion); this target was used for cueing secondary sequential point-to-point extension movements, as described below. All targets described 2.4° of rotation about the elbow, or ± 1.2° about each target location.

Primary Experimental Tasks:

Participants learned and performed six experimental tasks designed to quantify coordination of sequential stabilization and movement control actions. S*tabilizations* required participants to attempt to maintain forearm position at a target location against small perturbing forces. *Movements* required participants to either flex or extend the elbow in order to move between spatial target locations. The six tasks required stabilizations or movements in isolation, or a series of two or more actions in selected sequential combinations.

During the *stabilization* task, participants viewed a cursor that gave veridical, real time feedback of hand position and the desired target while the handle was perturbed by a 5-second, sum-of-sinusoids torque signal (sum of 2.1- and 3.5-Hz sinusoids; 2 Nm peak to peak). Participants were instructed to keep the cursor inside the target (center of target ± 1.2°) for the duration of the stabilization period, and were provided the on-screen instruction to "STABILIZE!".

During the *movement* task, participants were instructed to perform a point-to-point elbow movement between pairs of spatial targets as quickly and accurately as possible (Figure 1B). In the movement task, participants were cued to move when the screen displayed the home target, the goal target, a cursor showing veridical hand position, and an instruction to move, such as "FLEX!". Cursor feedback was eliminated once the arm had moved 20% of the distance between the targets to prevent reliance on visual feedback during movement. Cursor feedback was reinstated when the arm had moved more than 80% of the distance between the home and goal targets. After completing a movement trial, participants viewed feedback of peak velocity achieved

during the trial and feedback of the location of the hand when velocity first reached zero after movement initiation.

In the remaining four tasks, we required participants to perform sequential combinations of the movement and stabilization tasks. We constrained the initial or final conditions of a point-to-point elbow flexion movement by requiring participants to stabilize the arm against robotic perturbation just prior to, or just after, the movement task was completed. In a third combined task (the reversal task), we constrained the final conditions of the point-to-point elbow flexion movement by requiring participants to perform a point-to-point extension movement immediately after the initial flexion movement. In each of the conditions in which stabilization preceded a point-to-point flexion movement, the movement was cued approximately 250 ms after the end of perturbation. In conditions where stabilization was cued after movement, the stabilization period was initiated as soon as the movement completion conditions were met (i.e., the participant had moved at least 80% of the required distance and the hand had stopped moving). Adding these components to the basic feedforward point-to-point movement task allowed us to examine the impact of an explicit feedback task and sequential-task planning on the performance of the basic point-to-point elbow flexion task and to examine the impact of sequential-task planning on performance of the basic stabilization task. In the text that follows, we refer to the six task combinations as: stabilize (S, Fig. 4.1C), flex (FLX, Fig. 4.1D), flex then stabilize (FLX-S, Fig. 4.1E), stabilize then flex (S-FLX, Fig. 4.1F), reversal (i.e., flex-extend, REV, Fig. 4.1G), and stabilize then reversal (S-REV, Fig. 4.1H).

Participants performed blocks of six trials of each task type to acclimate to the six task conditions. After the acclimation period, they performed the tasks in a mixed training phase in which they performed eight trials of each of the six task types using randomized, paired trials, i.e., two trials of the same task type were presented in succession, and then the task type was changed for the next two trials. Trials were paired so that participants could immediately use feedback from the first trial of a pair to modify performance on the second. Finally, in the performance assessment phase, participants performed blocks of 12 trials of each task type. The order of blocks within the performance assessment phase was randomized between participants to prevent order effects.

Data Analyses

All kinematic measures were calculated relative to θ_{home}. Elbow joint kinematic data were low-pass filtered with a zero-lag, 4th order Butterworth filter (4 Hz cutoff frequency), then divided by the distance between θ_{home} and θ_{goal} (Δ_{goal}) to yield a normalized measure of flex target distance across participants (see Table 4.1 for flex target distance, θ_{goal}, in degrees), yielding normalized position values where 0% Δ_{goal} describes the center of θ_{home}, 100% Δ_{goal} describes the center of θ_{goal}, and negative values would describe extension of the arm beyond θ_{home}. When normalized, target width is ± 4% Δ_{goal}. Normalizing the position data in this manner allows us to compare performance across participants despite some participants having limited range of motion. Velocity and acceleration were derived from the normalized position data.

For stabilization tasks, we examined the mean normalized joint angle ($\mu_{stabilize}$) and standard deviation of normalized joint angle ($\sigma_{stabilize}$) for the last 500 ms prior to the

end of the mechanical perturbation (see Figure 4.2A and B, dark gray box). For point-to-point elbow flexion movements, we defined the start of movement, t_{start}, the time when the elbow joint velocity first reached 10% of its peak value (see Fig. 4.2 A and B, bright green line). We defined the end of movement, t_{end}, to be the time when two criteria were simultaneously met: the elbow-joint velocity dropped below 10% of peak velocity and at least 80% of the target distance had been achieved (see Fig 4.2 A and B, red line). Execution time (ET) was defined as the time elapsed between the t_{start} and t_{end}. We also identified two position error measures for the movement, the first measure (ε_{prior}) was taken 150 ms prior to t_{start}, and the second was position error at t_{end} (ε_{end}).

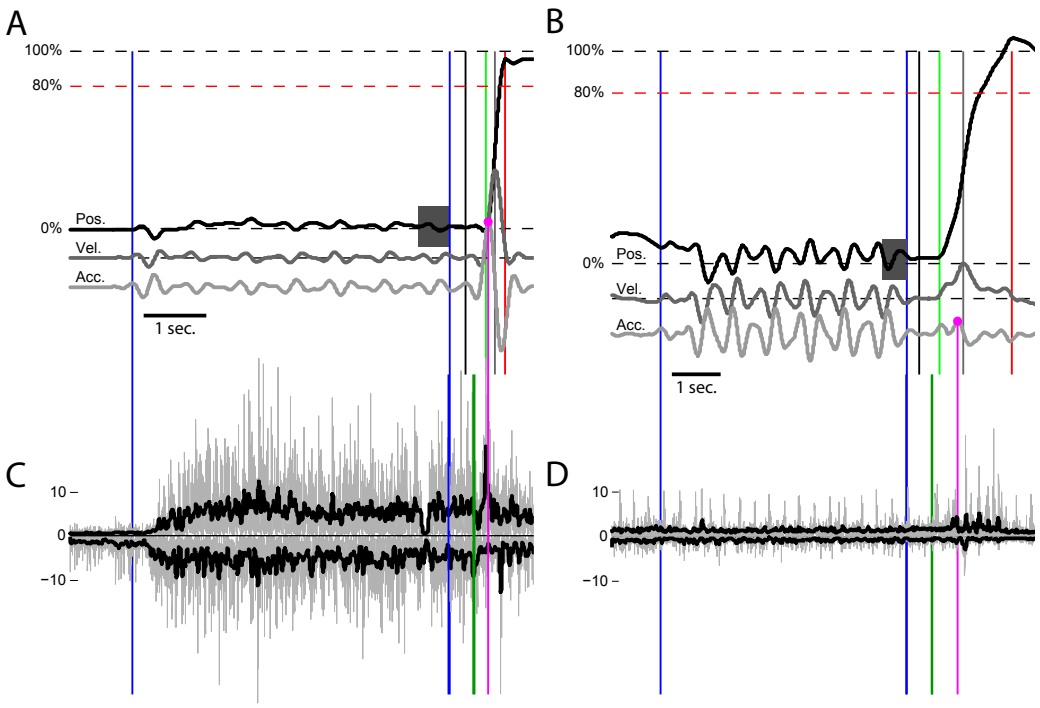

Figure 4.2: Normalized kinematic and electromyographic performance for selected trials of NI09 (A) and SP114 (B) performing the S-FLX task. In A and B, position, velocity and acceleration data are normalized to the distance between θ_{home} and θ_{goal} (% Δ_{goal}). Position: solid black line depicts measured handle position. Stabilization portion: vertical blue lines indicate start and end of mechanical perturbation of the hand. Gray box depicts 500 ms window in which kinematic stabilization performance was analyzed. Black vertical line indicates time of "go" cue for "flex" portion of the trial. Green and red vertical line indicates start and end of movement, respectively. Horizontal dashed red line indicates spatial movement completion threshold, horizontal black dashed line indicates target. Velocity: Medium gray trace depicts velocity derived from measured handle position. Vertical gray line depicts velocity peak used for further analysis (see below). Acceleration: Light gray line depicts acceleration. Pink dot indicates acceleration peak immediately prior to selected velocity peak. C: EMG recorded from NI09 during S- FLX trial; D: EMG recorded from SP114 during S- FLX trial. For both C and D panels, upper trace is the selected flexor, lower trace is the selected extensor (inverted). Light gray traces are zero-mean rectified EMG signals, black traces are normalized, low-pass filtered EMG signals used for analysis. Blue line indicates EMG window for stabilize, green line indicates EMG window ending 150 ms prior to movement start, and magenta line indicates EMG window prior to A_{pk}.

It has been noted that SP frequently use a strategy of multiple submovements (also called movement units) characterized by a multiphasic velocity profile when performing point-to-point movements instead of a single movement characterized by a smooth, bell-shaped velocity profile (Krebs 1999, Cirsea and Levin 2000, McCrea and Eng 2005, Rohrer et al. 2002, Dipietro et al. 2009, Trombly 1992, Kamper et al. 2002). In

order to investigate the relationship between sequential tasks, we modeled submovements using the velocity trace and then integrated the modeled velocity profiles to estimate expected changes in joint angle due to each submovement. We began with the assumption that peaks in the velocity profile are related to the number of submovements. Since these inflections can be very subtle, we used an approach similar to that of Fishbach and colleagues (2005) that exploits the relationship between velocity and its second derivative, jerk, which has a pair of zero crossings associated with each velocity peak, however subtle. The number of pairs of zero crossings in the jerk trace was used as a first estimate of number of submovements (N_{SM}). We then used a constrained non-linear optimization algorithm (`fmincon`, MATLAB, MathWorks, Natick, MA) to characterize the means, amplitudes, and standard deviations of a set of N_{SM} Gaussians in order to minimize the sum of squared error between the model (sum of N_{SM} characterized Gaussians) and the velocity profile derived from the measured position. Goodness of fit was evaluated based on variance accounted for (Eq. 1, Scheidt et al. 2001).

$$VAF = 1 - \frac{var(residuals)}{var(data)}, \qquad \text{[Eq. 1]}$$

The output was visually verified and N_{SM} was manually adjusted and the optimization model was run again if the model accounted for less than 95% of variance in the velocity trace. Across all trials, the average variance accounted for by the model was 98.8%.

The first submovement can be assumed to be feedforward because it was executed before any knowledge of outcome could be obtained, thus we focused further analyses on the first submovement to examine the impact of sequential-task planning on the performance of the basic point-to-point elbow flexion task. Specifically, the amplitude of the first Gaussian was the peak velocity of the first submovement (v_{pk}, Fig 4.3, top

panels). The integral of the first Gaussian was used to reconstruct change in joint angle due to the initial submovement (i.e. the distance of the first submovement, Δ_{SM1}; Fig 4.3, top panels), which was combined with the elbow angle at the start of movement to calculate the error at the end of the first movement unit (ε_{SM1}).

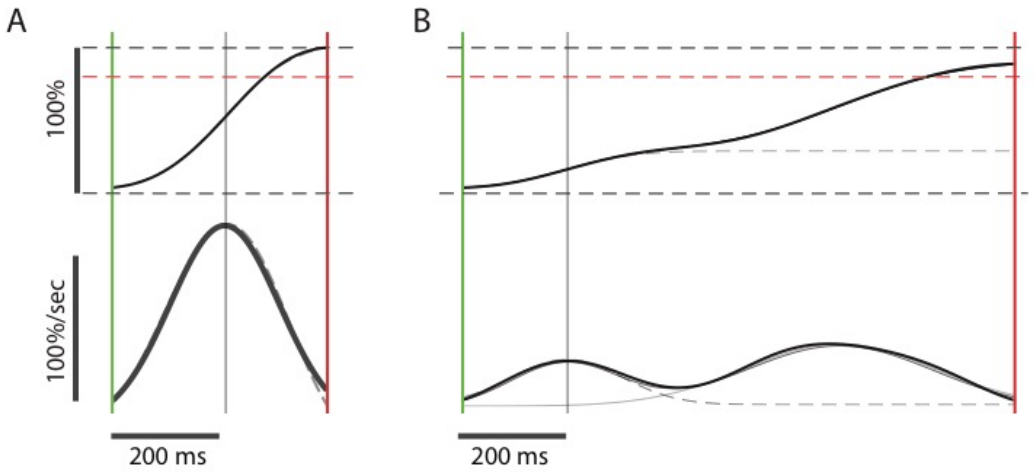

Figure 4.3: Submovement modeling of flexion task, one NI flexion (A), and one SP flexion (B) expanding on the transition window from start of movement (vertical green line) to movement end (vertical red line). Vertical gray line depicts location of velocity peak of first modeled submovement. Top: lower and upper horizontal black dashed line indicate θ_{home} and θ_{goal}, respectively. Dashed horizontal red line indicates 80% distance threshold required for task completion. Solid black curve depicts measured handle position, light gray dashed curve indicates final position estimated from first modeled submovement (note: this curve largely overlaps the measured data in A), solid gray (overlapping black) line indicates complete modeled handle position as sum of all integrated, modeled submovement velocity profiles. Bottom panels show measured and modeled velocity traces. Solid black is velocity trace derived from measured handle position, dashed gray curve is modeled velocity profile for first submovement, solid gray curve is shown for subsequent submovements.

Coordination measures

We calculated two measures to examine the influence of sequential-task execution on stabilization and movement control actions. To quantify changes in stabilization control actions related to upcoming movement, we calculated the change between hold

variability during last 500 ms of perturbation ($\sigma_{stabilize}$) in the simple stabilize task and during stabilize tasks which were followed immediately by a point-to-point elbow flexion. Specifically, we calculated $\Delta\sigma_{stabilize}$ by taking the average of $\sigma_{stabilize}$ in the isolated stabilization task (S) and subtracting from it the average $\sigma_{stabilize}$ for stabilize tasks followed immediately by a point-to-point elbow flexion movement (S-FLX and S-REV) as shown in equation 2,

$$\Delta\sigma_{stabilize} = \overline{\sigma^{S}_{stabilize}} - \frac{\overline{\sigma^{S,FLX}_{stabilize}} + \overline{\sigma^{S,REV}_{stabilize}}}{2} . \qquad \text{[Eq. 2]}$$

Similarly, to quantify changes in point-to-point movement control actions due to the presence of prior limb stabilization, we calculated the difference in number of submovements to complete the targeted elbow flexion task. Specifically, we calculated ΔN_{SM} by taking the average N_{SM} in the isolated elbow flexion task (FLX) and subtracting from it the average N_{SM} for elbow flexion tasks immediately preceded by stabilizations (S-FLX and S-REV) as shown in equation 3,

$$\Delta N_{SM} = \overline{N^{FLX}_{SM}} - \frac{\overline{N^{S,FLX}_{SM}} + \overline{N^{S,REV}_{SM}}}{2} . \qquad \text{[Eq. 3]}$$

EMG:

Digitized EMG signals were notch-filtered at 60, 120, and 180 Hz ± 10 Hz (zero-lag, 3rd order Butterworth), zero-meaned, rectified, and low-pass filtered at 20 Hz (zero-lag, 2nd order Butterworth). EMG signals from MVE trials were processed as above and then subjected to a 100 ms moving average filter, after which the maximal value for each muscle was determined. Then for each muscle and each trial, the EMG signal was normalized to (i.e., divided by) the maximal value obtained from that muscle from MVE

testing. We selected a single flexor and extensor by computing signal-to-noise ratio (SNR) between the maximal contraction condition and the resting baseline condition during pre-trial MVE collection (see Table 4.1). We selected the flexor and extensor muscle with the greatest SNR for further analysis. The selected muscle varied across participants (cf. McCrea et al. 2003, Kautz and Brown 1998, Canning et al. 2000).

Secondary measures of coordination of agonist/antagonist muscle activation magnitude were calculated using primary flexor and extensor EMG activity from each trial. Co-activation (CoA, Fig. 4.2C, D), is a measure the amount of instantaneous EMG activity that is equal and opposite in the agonist/antagonist muscle pair, defined in equation 4,

$$CoA(t) = \min(flexor(t), extensor(t)). \qquad [Eq. 4]$$

While CoA can be task-appropriate when increased limb impedance is desirable (e.g., stabilizing the arm against a perturbation), CoA measured during movement can be taken as a measure of the "wasted activation" (cf. Thoroughman and Shadmehr 2000) as the muscle activity does not contribute to motion of the limb segment. Difference activation (DiffA, Fig. 4.2C, D), quantifies the instantaneous phasic activation in the agonist/antagonist pair, defined in equation 5,

$$DiffA(t) = flexor(t) - extensor(t). \qquad [Eq. 5]$$

Net phasic muscle activation is required to move the limb segment in either flexion (positive DiffA) or extension (negative DiffA).

We used CoA and DiffA to quantify the temporal coordination between antagonist muscles spanning the elbow joint. Specifically, we averaged these measures for three, 50 ms epochs to investigate muscle coordination during stabilization, during a resting period

prior to movement, and during the first feedforward flexion movement. The first epoch evaluated was the final 50 ms of perturbation in the stabilize tasks ($CoA_{stabilize}$, Figure 4.2C, D blue bars). The second epoch began when the arm was at rest 200 ms prior to the start of the first submovement (CoA_{prior}, green bar, Figure 4.2 C, D). The final epoch was immediately prior to the acceleration peak associated with the first submovement (CoA_{pk} and $DiffA_{pk}$, magenta bar, Fig. 4.2C, D).

Statistical Hypothesis Testing

The current study had two specific objectives. The first was to quantify the extent to which stroke impairs control and coordination of limb position and movement. The second objective was to test the hypothesis that deficits of coordination between the control of limb position and limb movement correlate significantly with motor impairment and deficits of motor function after stroke.

Due to the broad range of impairment within our small cohort of stroke participants, and the ensuing high performance variability, we used a non-parametric approach for our primary statistical analyses: first, we applied a rank-transform (RT Type 1; Conover and Iman 1981) in which each data point for a given variable was ranked from smallest to largest across all instances across all participants with the mean rank being assigned in the case of ties. Ranks were then standardized by the number of instances to limit the distribution to strictly between 0 and 1. Finally, the standardized ranks were subjected to an inverse normal transform (Leupsen 2016; `Idf.Normal` function; IBM SPSS Statistics 24). This process is described in equation 6:

$$INT = \mathbf{\Phi}^{-1}(R_i/(n+1)), \qquad \text{[Eq. 6]}$$

where R_i is the rank of a given instance of the dependent variable, n is the number of instances, and $\mathbf{\Phi}^{-1}$ is the inverse normal transformation. These transformations enabled us to run parametric statistical tests on the ranked and transformed data (cf., Laczko et al. 2017). The INT-RT1 approach takes advantage of both between and within block information, resulting in a distribution-free test that compares favorably with Fischer's randomization test and the Friedman test in terms of power and robustness (Leupsen 2016, Conover and Iman 1981). It has also been demonstrated to be acceptable for assessing interactions (Conover and Iman 1981). ANOVA was used on the INT-RT1 variables as described below. Participant was included as a random factor in all ANOVA models. Post hoc tests were performed where indicated by ANOVA. Bonferroni *t*-tests were used for main group effects to test each group against all other groups. Dunnett *t*-tests used for main trial type effects to test composite conditions against the control conditions of FLX or S.

To address the first objective, we planned to first use INT-RT1 independent samples *t*-tests to examine group differences {NI, SP} in performance variables $\{\sigma_{stabilize}\}$, and $\{\varepsilon_{prior}, \varepsilon_{end}, N_{SM}, ET, v_{pk}, \Delta_{SM1}, \varepsilon_{SM1}\}$ from the single-task S and FLX trial types, respectively. We next used correlation analysis to quantify the relationship between stroke-related motor impairments $\{FM_M, \tau_{max}, MAS\}$, mild cognitive impairments {MoCA}, and somatosensory impairments $\{FM_P, FM_{LT}, AMDT\}$and performance measures specific to stabilization control $\{\sigma_{stabilize}\}$ and flexion movement control $\{N_{SM}, ET, v_{pk}, \Delta_{SM1}\}$ in SP. Upon finding extensive correlation between somatosensory impairment measures in SP and all of the selected position and movement control action

measures tested (see Results), we split the SP group into SP+ (intact proprioception, FM_P score of 6/6) and SP- (impaired proprioception, FM_P score <6).

We then continued with planned INT-RT1 ANOVA to quantify the extent to which somatosensory deficits after stroke affect coordination of sequential position and movement control actions. Specifically, our first ANOVA model tested for main effects of group {NI, SP+, SP-} and trial type {S, S- FLX, S-REV} on one stabilization performance variable $\{\sigma_{stabilize}\}$. A second ANOVA model tested for main effects of participant group {NI, SP+, SP-} and trial type {FLX, REV, FLX -S, S- FLX, S-REV} on each of four performance variables related to targeted elbow flexion: $\{N_{SM}$, ET, v_{pk}, $\Delta_{SM1}\}$. We were specifically interested in the extent to which impairments in proprioception might explain deficits observed in coordination of elbow stabilization and targeted elbow flexion.

We next planned to use INT-RT1 ANOVA to quantify the relationship between neuromuscular coordination and performance during the stabilization and targeted elbow flexion tasks by analyzing measures of flexor/extensor coordination (CoA and DiffA) during stabilization, during a rest period prior to movement, and during elbow flexion. Specifically, we tested for main and interaction effects of group {NI, SP+, SP-} and trial type {S, S-FLX, S-REV} on one stabilization performance variable $\{CoA_{stabilize}\}$. We then planned to use INT-RT1 ANOVA to examine main and interaction effects of participant group {NI, SP+, SP-} and trial type {FLX, REV, FLX-S, S-FLX, S-REV} on each of three performance variables related to flexion of the arm: $\{CoA_{prior}$, CoA_{pk}, $DiffA_{pk}\}$. We were particularly interested in the extent to which measured varied across

participant group and trial type, and the extent to which they might explain results observed in kinematic performance variables.

To address our final objective, we used forward regression analysis to test the hypothesis that deficits in control of limb position and limb movement correlate significantly with motor impairment and deficits of motor function after stroke. This analysis was restricted to SP data only as NI participants are, by definition, normative. We began by calculating the correlations of all of the outcome measures from the FLX and S conditions of the experiment $\{\sigma_{stabilize}$, ET, N_{SM}, v_{pk}, $\Delta_{SM1}\}$ and the clinical measures described above $\{\tau_{max}$, MAS, MoCA, FM_P, FM_{LT}, AMDT$\}$. We then performed a forward regression using a subset of these variables to prevent overburdening the model with correlated measures, which would decrease detection power of the model (Cohen and Cohen 1983). Specifically, we used $\{\tau_{max}$, MAS, MoCA, FM_P, FM_{LT}, AMDT v_{pk}, and $\sigma_{stabilize}\}$ to evaluate the extent to which stroke-related deficits of coordination between the control of limb position and movement account for variance in impairment, as quantified by FM_M, and deficits of motor function, as quantified by CAHAI.

All statistical testing was performed in the SPSS computing environment (SPSS ver. 24, IBM Corp). Effects were considered significant using a familywise error rate of $\alpha = 0.05$. Values reported are (Mean ± SD).

RESULTS

This study had two specific objectives: The first was to quantify stroke-related changes in control and coordination of limb position stabilization and limb movement. The second objective was to test the hypothesis that deficits of coordination between the

control of limb position stabilization and limb movement correlate significantly with motor impairment and deficits of motor function after stroke. We tested participants' ability to execute and coordinate two types of control actions: point-to-point elbow movements and stabilizing the elbow against a perturbation. These two control actions were combined to create six task types each consisting of between one and three control actions designed to test how participants coordinate sequential position stabilization and movement control actions in the upper extremity.

All participants were attentive and followed task instructions during the experimental sessions. Although performance varied considerably within the SP group, all participants were able to successfully perform all six task conditions. A trial was considered "good" if the participant complied with specific task instructions (i.e., flexed, stabilized, or extended the elbow when cued) and was able to complete the series of stabilization and movement actions required within the time window of 17 seconds after trial start. For these reasons, we excluded 4.4% of trials across all SP and 2.4% of trials across all NI. Compared with NI performance, SP had greater variability during stabilization, took longer to complete the flexion task, and were more likely to make multiple submovements with slower peak velocity (Fig. 4.4).

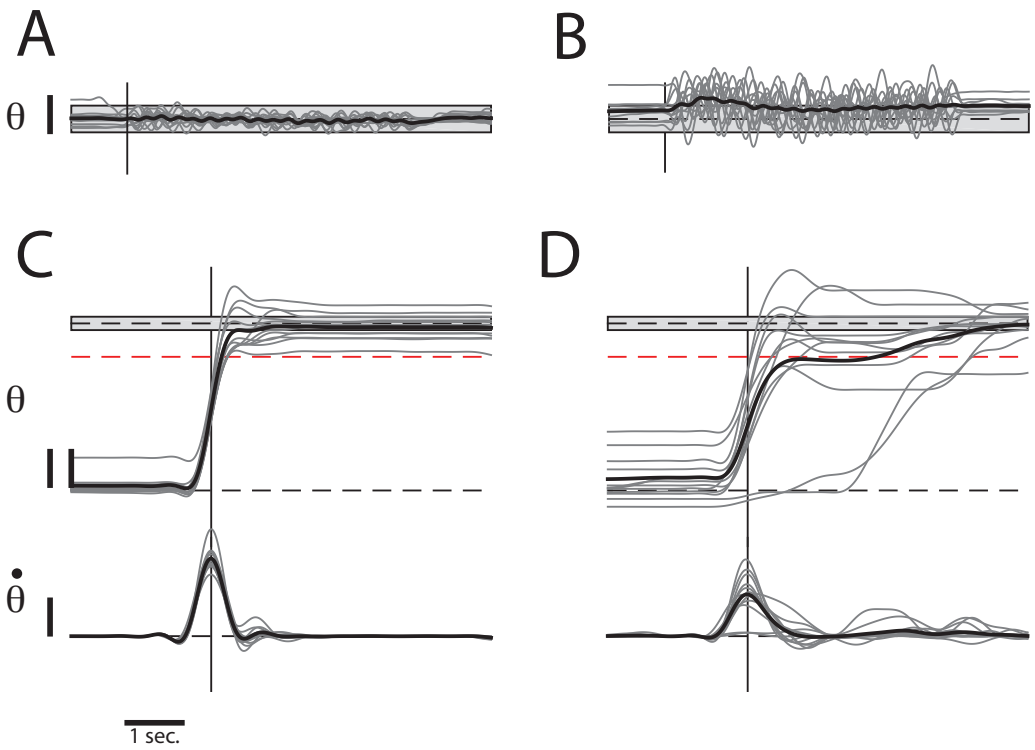

Figure 4.4: Kinematics for Stabilize and Flex in one NI (09) and one SP (114). In all panels, gray traces are individual trial data and black traces are averaged across trials. In each panel, the top plot is position (θ), in C and D, the lower plot is velocity ($\dot{\theta}$). All values are normalized to %Δgoal. In A and B, thick vertical line is 10% (position). In C and D, thick vertical line represents 20% (position), 200%/sec (velocity). Gray horizontal bar represents goal target for stabilization or flex with the specific target shown as a black horizontal dashed line in the center. The horizontal red dashed line shows the 80% to target value. The black dashed line (without shaded bar) shows 0%. A: Shows stabilization (S) trials for NI09. B: Shows stabilization (S) trials for SP114. C: Shows flex (FLX) trials for NI09. D. Shows flex (FLX) trials for SP114.

Impact of stroke on stabilization and movement control in isolation

Consistent with our first objective, we wished to quantify the extent to which stroke-dependent deficits of neuromuscular coordination degrade ability to stabilize and move the arm about the elbow. We therefore compared performance in the S and FLX tasks across SP and NI using INT-RT1 independent samples *t*-tests on each of the kinematic performance variables: $\{\sigma_{stabilize}, \varepsilon_{prior}, ET, N_{SM}, v_{pk}, \Delta_{SM1}, \varepsilon_{SM1}$, and $\varepsilon_{end}\}$. In

the stabilization task, we found that compared with NI, SP had greater variability in joint angle when stabilizing the elbow against perturbation ($\sigma_{stabilize}$; SP: 5.85 ± 3.50 $\%_{goal}$; NI: 1.89 ± 0.36 $\%_{goal}$; $t(19) = -3.534$, $p = 0.002$; Fig. 4.5 A). During the point-to-point movement FLX task, compared with NI, SP demonstrated static flexion bias prior to movement (ε_{prior}; SP: 16.88 ± 9.11 $\%_{goal}$; NI: 0.28 ± 1.19 $\%_{goal}$; $t(19) = -4.906$, $p < 0.0005$; Fig. 4.5B). Additionally, SP required more time to complete the flexion task than did NI (ET; SP: 1295 ± 705 ms; NI: 426 ± 156 ms; $t(19) = -4.913$, $p < 0.0005$; Fig. 4.5C). SP also made more submovements during the targeted elbow flexion task than did NI (N_{SM}; SP: 2.52 ± 1.46 SM; NI: 1.12 ± 0.18 SM; $t(19) = -3.586$, $p = 0.002$; Fig. 4.5D). Consistent with longer execution times and greater number of submovements, SP also had lower peak velocity during the first submovement than did NI (v_{pk}; SP: 166 ± 87 $\%_{goal}$/sec; NI: 465 ± 135 $\%_{goal}$/sec; $t(19) = 6.106$, $p < 0.0005$; Fig. 4.5E). Unsurprisingly, the slower first submovement made by SP also covered less distance than the first submovement made by NI (Δ_{SM1}; SP: 53.87 ± 29.23 $\%_{goal}$; NI: 98.61 ± 7.29 $\%_{goal}$; $t(19) = 4.402$, $p < 0.0005$; Fig. 4.5F). SP also had correspondingly greater undershoot error at the end of the first submovement compared with NI (ε_{SM1}; SP: -28.78 ± 26.21 $\%_{goal}$; NI: -2.68 ± 5.47 $\%_{goal}$; $t(19) = 2.560$, $p = 0.019$; Fig. 4.5G). Despite the differences prior to and during movement, we observed no difference in error at the end of the flexion task between SP and NI (ε_{end}; SP: 3.94 ± 9.70 $\%_{goal}$; NI: -0.53 ± 4.35 $\%_{goal}$; $t(19) = -1.090$, $p = 0.289$; Fig. 4.5H). These results indicate that while participants from both groups were ultimately able to successfully complete the flexion and stabilization tasks, there were marked differences in how the task was completed between groups, as well as high variability within the SP group.

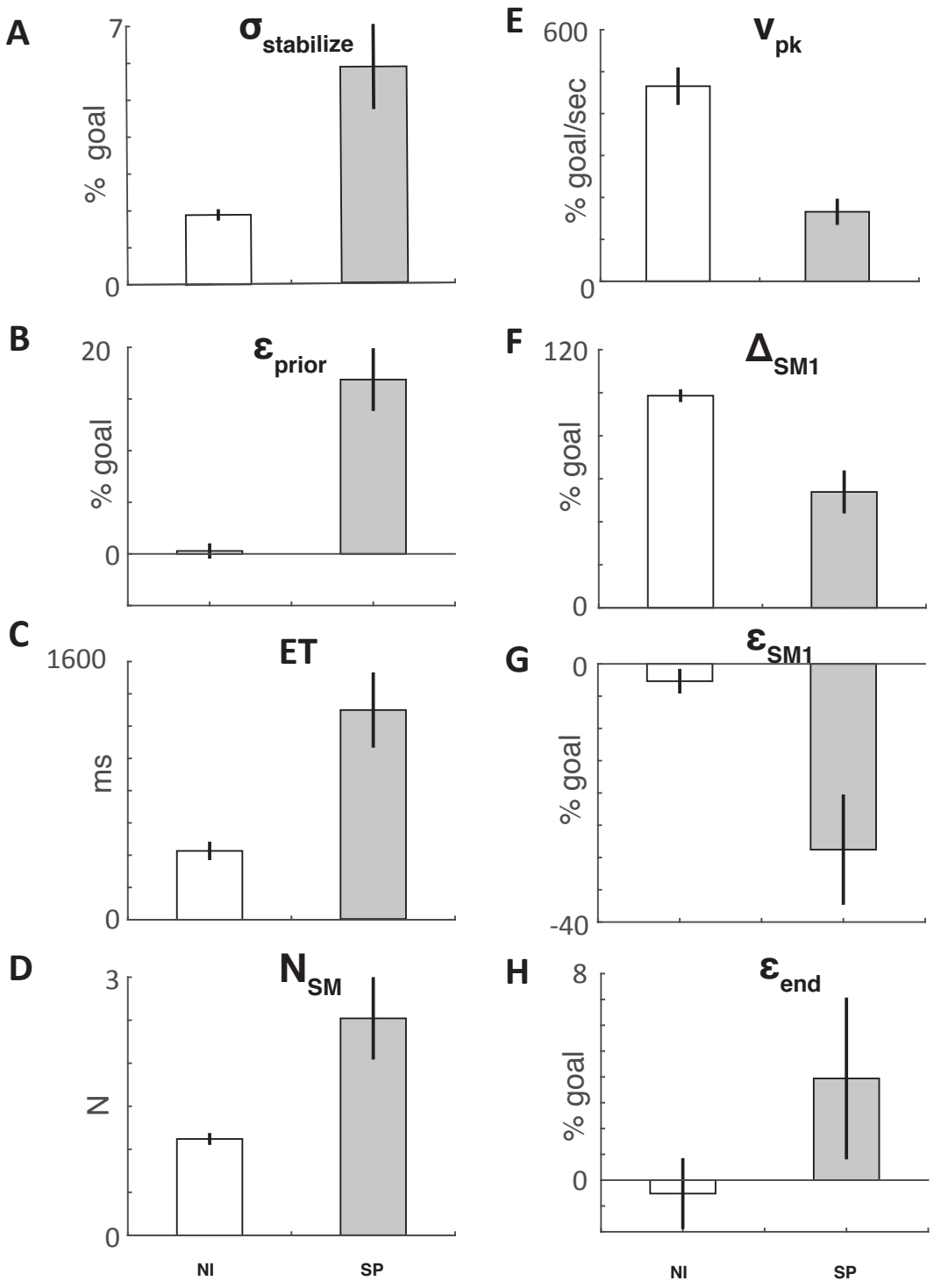

Figure 4.5: Kinematic performance of NI and SP during S and FLX tasks. White bars indicate NI, gray bars indicate SP. Error bars denote ± 1 S.E.M. A: standard deviation of position during stabilize in % goal ($\sigma_{stabilize}$); B: Error during rest prior to movement in %goal (ε_{prior}); C: Execution time for flexion task in ms (ET); D: Number of submovements required to complete flexion task (N_{SM}); E: Peak velocity of first submovement in % goal/sec (v_{pk}); F: Error at end of first submovement in % goal (ε_{SM1}); G: Error at end of flexion task in % goal (ε_{end}).

Relationship of specific, stroke related deficits on stabilization and movement control

Given the high levels of variability observed in how SP completed the S and FLX tasks, we next sought to quantify the extent to which specific stroke-related motor, cognitive, and sensory impairments impacted performance measures of stabilization and movement. Specifically, we used correlation analysis to quantify the relationship between measures of motor impairment {FM_M, τ_{max}, MAS}, mild cognitive impairment {MoCA}, and somatosensory impairment {FM_P, FM_{LT}, AMDT} and the experimental outcome measures of position {$\sigma_{stabilize}$} and movement {ET, N_{SM}, v_{pk}, and Δ_{SM1}} control actions. For the stabilization measure, values were included from {S, S-FLX, and S-REV}; values from FLX-S were excluded as the stabilization in this condition was performed at a different handle location, which could impact performance (Levin 2000). For the movement measures, values were included from all conditions with a flexion component: {FLX, REV, S-FLX, S-REV, and FLX-S}. Results are reported in Table 4.2.

Table 4.2: Correlations between impairment measures and outcome measures.

	CAHAI	FM_M	τ_{max}	MAS	MoCA	FM_P	FM_{LT}	AMDT	σ_{stabil}	ET	N_{SM}	v_{pk}	Δ_{SM1}
CAHAI	1												
FM_M	.812***	1											
τ_{max}	.681***	.618***	1										
MAS	-.234	-.568***	-.158	1									
MoCA	.235	-.138	.376**	.111	1								
FM_P	.455***	.053	.273*	.204	.556***	1							
FM_{LT}	.473***	.091	.471***	.041	.559***	.791***	1						
AMDT	-.468***	-.066	-.398**	-.093	-.874***	-.667***	-.550***	1					
$\sigma_{stabilize}$	-.414*	-.106	-.216	-.136	-.575**	-.567**	-.303	.597***	1				
ET	.103	.052	.212	.028	.099	.440**	.621***	-.150	.296	1			
N_{SM}	.121	.015	.200	.024	.132	.498***	.682***	-.215	.209	.971***	1		
v_{pk}	-.097	-.016	-.291*	-.010	-.085	-.336*	-.693***	-.037	-.247	-.743***	-.739***	1	
Δ_{SM1}	-.260	-.023	-.441**	-.097	-.222	-.489***	-.809***	.240	-.167	-.722***	-.780***	.874***	1

*Correlation significance: * (0.05 level); ** (0.01 level); *** (0.001 level).CAHAI, 13-item Chedoke Arm and Hand Activities Inventory; FM_M, motor portion of upper extremity Fugl-Meyer Assessment (FMA); τ_{max}, average maximal elbow torque MAS, Modified Ashworth Scale of muscle tone; MoCA, Montreal Cognitive Assessment; FM_P, proprioception portion of FMA; FM_{LT}, light-touch portion of FMA; AMDT, arm movement detection test; σ_{stabil}, standard deviation of arm position during stabilization; ET, execution time of flexion movement; N_{SM}, number of submovements to complete flexion movement; v_{pk}, peak velocity of first submovement; Δ_{SM1}, distance of first submovement.*

Maximal torque production at the elbow was the only motor impairment measure that that correlated significantly with any of the *motor outcome measures*, specifically v_{pk} (r = -0.291, p = 0.040) and Δ_{SM1} (r = -0.441, p = 0.001). Mild cognitive impairment was found to correlate significantly with $\sigma_{stabilize}$ (r = -0.575, p = 0.001). Every outcome measure of position and movement control actions was correlated with multiple measures of *somatosensory* impairment: FM_P was significantly correlated with all stabilization and movement measures tested $\{\sigma_{stabilize}$, ET, N_{SM}, v_{pk}, and $\Delta_{SM1}\}$, $|r| \geq 0.336$, $p \leq 0.017$ in all cases. FM_{LT} was significantly correlated with all movement measures tested (ET, N_{SM},

v_{pk}, and Δ_{SM1}), $|r| \geq 0.621$, $p < 0.0005$ in all cases. AMDT was significantly correlated with the tested measure of stabilization control, $\sigma_{stabilize}$, $r = 0.597$, $p < 0.0005$.

Given the strong relationship between measures of somatosensory impairment and all of the positional and movement control action measures, we used FM_P to split the SP group into those with "intact" (SP+, participants scoring 6/6 on FM_P) and "impaired" proprioception (SP-, participants scoring ≤ 5 on FM_P). We chose FM_P rather than FM_{LT} or AMDT as it correlated with all of the control action performance measures.

Impact of stroke-related deficits on coordination of sequential tasks

To further investigate our first objective, we wished to quantify the extent to which stroke-related impairments impacted coordination of positional stabilization control actions and movement control actions in sequential tasks consisting of elbow stabilizations and movements (i.e., targeted elbow flexions). We began by using INT-RT1 ANOVA to examine the main and interaction effects of participant group {NI, SP+, SP-} and task type {S, S-FLX, S-REV} on $\sigma_{stabilize}$, a measure of positional stabilization control. We found a main effect of group [$F_{(2,18)} = 13.343$, $p < 0.0005$], and of task type [$F_{(2,36)} = 22.254$, $p < 0.0005$]. Among the groups, NI had less variability during stabilization than either SP group ($p < 0.0005$ in both cases, Fig. 4.6) and SP+ had less variability during stabilization than did SP- ($p < 0.0005$). Among trial types, there was greater variability in stabilization prior to point-to-point flexion (S_FLX, S_REV) than there was during stabilization alone (1-sided Dunnett with the S condition as control: $p < 0.0005$ in both cases). Taken together, these results indicate that impairments of proprioception degrade ability to stabilize the limb. Also, participants in all groups were

less able to stabilize the arm when planning an upcoming movement vs. when they had no immediate tasks to perform.

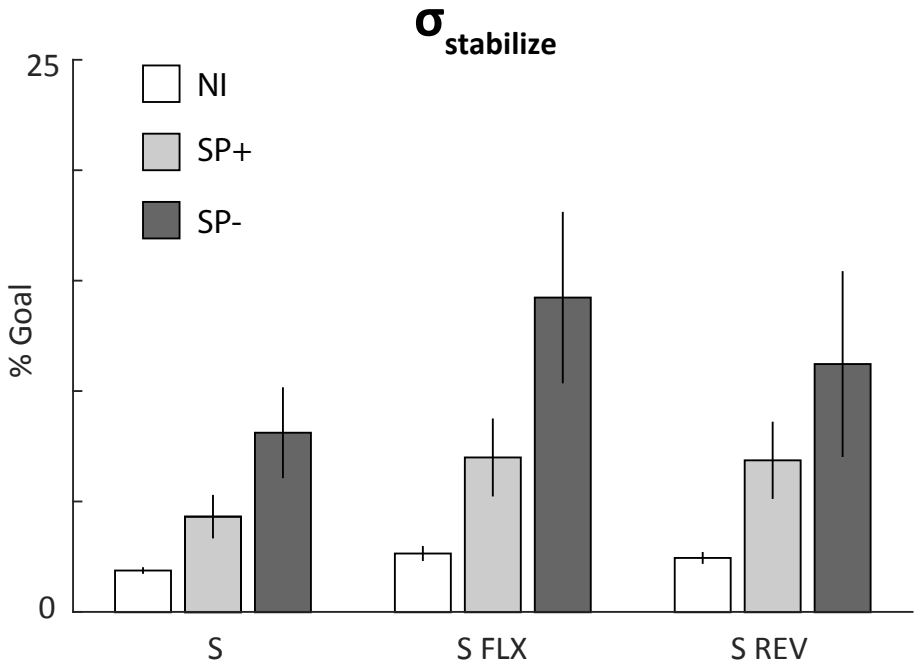

Figure 4.6: Impact of planned movement on stabilization. White bars represent NI, light gray bars represent SP+, dark gray bars indicate SP-. Error bars indicate± 1 S.E.M.

We next used INT-RT1 ANOVA to test for main and interaction effects of participant group {NI, SP+, SP-} and task type {FLX, S-FLX, S-REV, FLX-S, REV} on the performance measures sensitive to movement control (i.e., ET, N_{SM}, v_{pk}, and Δ_{SM1}). We observed a significant main effect of participant group in ET [$F_{(2,18)} = 14.150$, $p < 0.0005$ in all cases, Fig. 4.7A], with NI completing the flexion movement in less time than the SP-, who required less time than the SP+. For N_{SM}, we observed significant main effects of participant group [$F_{(2,18)} = 15.372$, $p < 0.0005$ across all groups, Fig. 4.7B], as well as a significant main effect of trial type [$F_{(4,72)} = 3.775$, $p = 0.008$] with the number

of submovements used to complete the flexion task greater in S-FLX compared to FLX ($p = 0.013$, 1-sided Dunnett). We observed a significant main effect of participant group on v_{pk} [$F_{(2,18)} = 16.495$, $p < 0.0005$ in all cases, Fig. 4.7C]. We also observed a main effect of participant group on the Δ_{SM1} [$F_{(2,18)} = 14.328$, $p < 0.0005$ in all cases, Fig. 4.7D]. Taken together, these results indicate that while performances in all SP were degraded compared to NI, the survivors of stroke with *intact* proprioception group showed *greater impairment* in executing movement control actions than did the survivors of stroke with *impaired* proprioception.

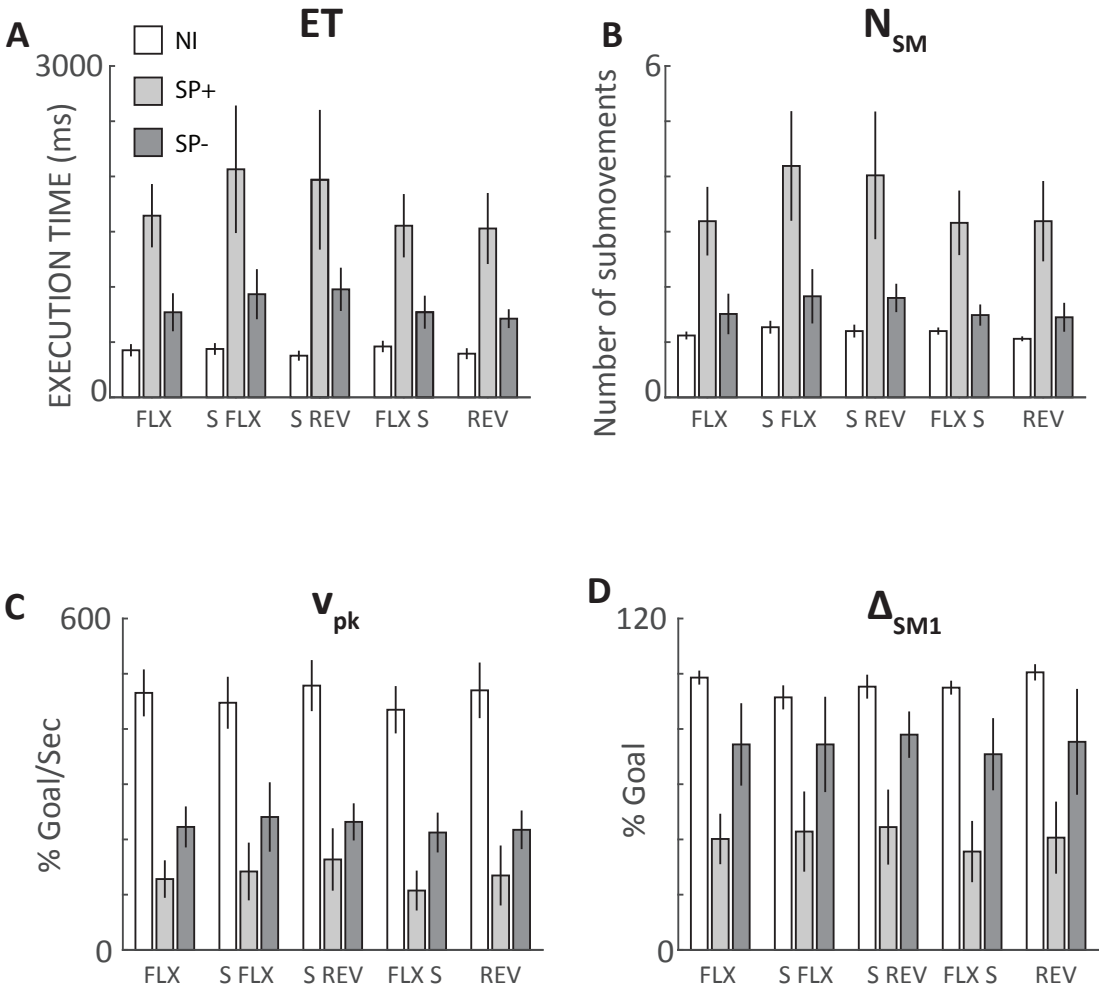

Figure 4.7: Coordination of sequential stabilize-movement actions on elbow flexion. White bars indicate NI, light gray bars indicate SP+, dark gray bars indicate SP-. Error bars indicate ± 1 S.E.M. A: Execution time (ET; ms); B. Number of submovements required to complete flexion task (N_{SM}); C: Peak velocity of submovement (v_{pk}; % goal/sec); D: Distance of first submovement (Δ_{SM1}; % goal).

Given that some participants in the SP group had shortened targets (θ_{goal}) compared to the standard 30º elbow flexion (see Table 4.1), we were concerned that the normalized speed and distance could be artificially inflated in these SP compared to those participants using the standard θ_{goal}. We checked our analyses of peak velocity and distance of first movement unit using raw values (º elbow flexion) to confirm that these findings were not an artifact of normalizing. The results of the raw values were consistent

with those of the normalized values for both v_{pk} and Δ_{SM1} [$F_{(2,18)} \geq 21.395$, $p < 0.0005$ in all cases]. Similar analyses were not run for ET and N_{SM} as both values are non-normalized. While both ET and N_{SM} could conceivably be decreased due to the shorter movement distance, we do not have empirical data to test this hypothesis.

Coordination of multiple control actions

To quantify the influence of executing sequential control actions on position and movement control, we used Kruskal-Wallis non-parametric testing of coordination measures $\{\Delta\sigma_{stabilize}, \Delta N_{SM}\}$ across each permutation of groups {NI, SP+, SP-}. Recall that $\Delta\sigma_{stabilize}$ is the difference between the average stabilization performances in the S condition vs. the two tasks with subsequent movement (i.e., S-FLX and S-REV), and ΔN_{SM} is the difference in the average number of submovements in the FLX task with the average number of submovements in the two tasks with preceding stabilizations (i.e., S-RCH and S-REV). We selected Kruskal-Wallis testing instead of INT-RT1 ANOVA for these analyses because the coordination measures were calculated from kinematic trial data averaged across each participant instead of from ranks of every trial performed by every participant. For $\Delta\sigma_{stabilize}$, we observed a significant effect of group between NI and both SP groups ($H^2 \geq 5.343$, $p \leq 0.021$), but not between SP groups ($H^2 = 1.1316$, $p = 0.286$; mean ranks: NI: 6.91, SP+: 14, SP-: 17.75). For ΔN_{SM}, we did not observe significant differences across groups ($H^2 \leq 2.063$, $p \geq 0.151$; mean ranks: NI: 8.82, SP+: 13.83, SP-: 12.75). While the trends observed in Fig. 4.8 are qualitatively similar to the prior observation that intact proprioception after stroke allows better performance during

stabilization and worse performance during movement, the results did not reach statistical significance with this cohort of SP.

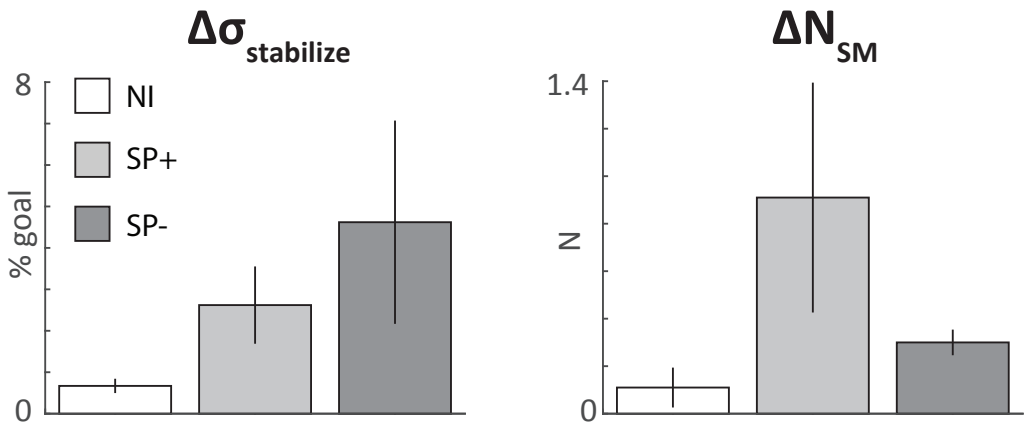

Figure 4.8: Coordination of sequential position-movement control actions. A: Change in position variability between stabilization (S) and stabilize/move tasks (S-FLX, S-REV). B: Change in number of submovements used to complete movement task between flexion task (FLX) and flexion tasks preceded by stabilization (S-FLX, S-REV).

Agonist/antagonist muscle coordination at the elbow during sequential stabilization and flexion tasks

We wished first to confirm that all participants were able to modulate their muscle activity above the resting level measured during "relax" portions of the MVE calibration procedures (RLX). Thus, we used INT-RT1 ANOVA to examine the main and interaction effects of participant group {NI, SP+, SP-} and task type {RLX, S, S-FLX, S-REV} on the amount of CoA present during RLX and $\{CoA_{stabilize}\}$. We observed a main effect of trial type ($F_{(4,68)} = 25.571$, $p < 0.0005$) with greater levels of CoA during stabilization than relaxation ($p < 0.0005$ in all cases, 1-sided Dunnett; Fig. 4.9A). This main effect was driven entirely by differences between relaxation and active stabilization in the NI group, as evidenced by a significant group by type interaction ($F(8,68) = 5.806$, $p < 0.0005$). In the NI group, all stabilization conditions {S, S-FLX, S-REV} were significantly different

from RLX ($p < 0.0005$ in all cases, 1-sided Dunnett). In both the SP+ and SP- groups, however, there were no significant differences between any of the active stabilization conditions and the relax condition ($p > 0.217$ in all cases, 1-sided Dunnett). Thus, while NI had significantly less CoA when relaxing than when actively stabilizing the arm against a perturbation, SP – regardless of proprioceptive status – had elevated CoA when relaxing to the extent that it was not significantly different from CoA measured when actively stabilizing the arm.

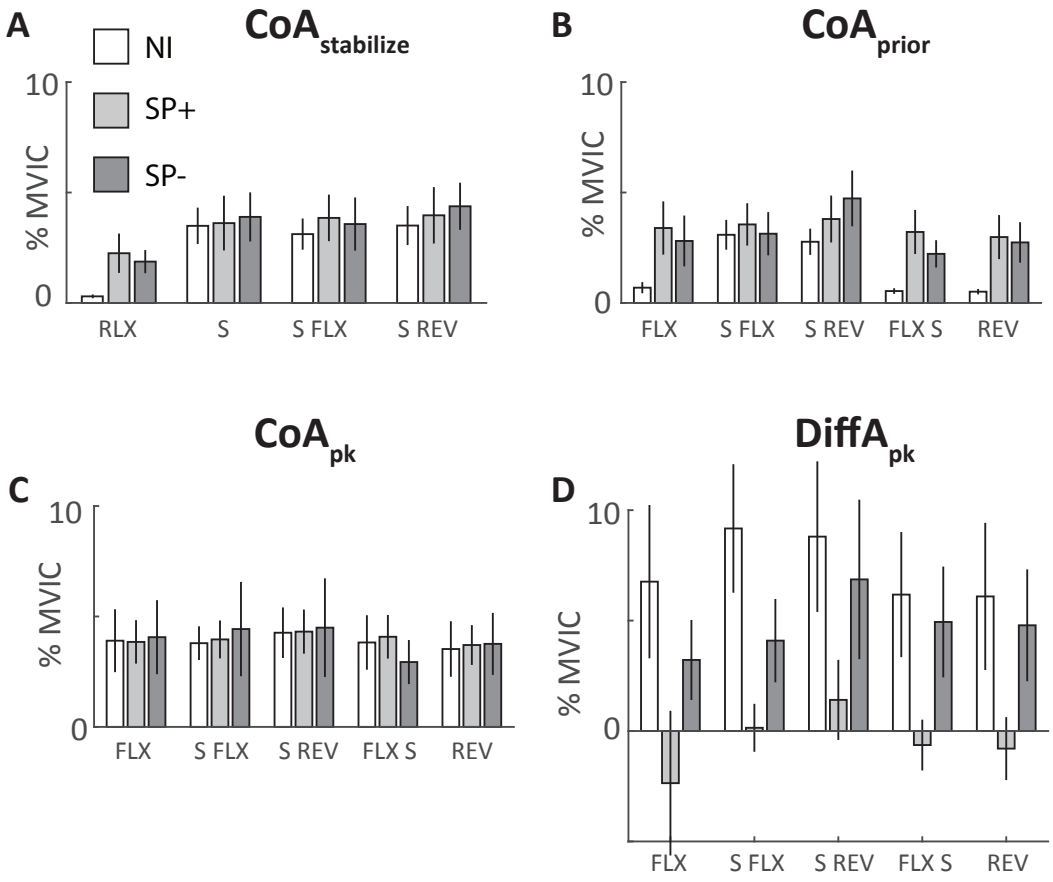

Figure 4.9: Coordination of selected elbow flexor and extensor during stabilization, rest before flexion, and flexion. White bars indicate NI, light gray bars indicate SP+; dark gray bars indicate SP-. Error bars indicate ± 1 S.E.M. A: Co-Activation during pre-trial relax and stabilization against perturbation; B: Co-Activation during rest prior to flexion; C: Co-Activation during flexion; D: Difference activation during flexion.

We next wished to quantify the extent to which prior perturbation impacted the amount of CoA observed prior to point-to-point movement and the impact of stroke on this measure. Thus, we used INT-RT1 ANOVA to examine main and interaction effects of participant group {NI, SP+, SP-} and task type {FLX, S-FLX, S-REV, FLX-S, REV} on the amount of CoA observed when the hand was at rest prior to movement $\{CoA_{prior}\}$. We observed a main effect of participant group [$F_{(2,17)} = 7.345$, $p = 0.005$; Fig. 4.8B] and of task type [$F_{(4,68)} = 19.792$, $p < 0.0005$], and an interaction effect between group and task type [$F_{(8,68)} = 7.467$, $p < 0.0005$].

We next completed follow-on 1-sided Dunnett *t*-tests to examine the hypothesis that CoA_{prior} would be elevated after stabilization compared to after rest. Specifically, we compared CoA_{prior} in {S-FLX, S-REV, FLX-S, REV} to that observed in point-to-point flexion {FLX} in individual groups {NI, SP+, SP-}. Results of this comparison indicate that the observed main effect of task type is due to differences in the NI group. In the NI group, participants had lower levels of CoA prior to flexion tasks preceded by rest compared to flexion tasks preceded by active stabilization (NI: COA elevated after stabilization compared to FLX: $p < 0.0005$ in both cases, 1-sided Dunnett; CoA same after pre-flex relax across FLX, FLX-S, REV, $p \geq 0.978$ in both cases). SP of both groups, however, had consistent levels of CoA_{prior} in all task types, regardless of whether they were stabilizing against a perturbation or relaxing prior to the flexion task ($p \geq 0.091$ in all cases, 1-sided Dunnett). This indicates that while NI participants were able to reduce activation in both the selected elbow flexor and extensor when stabilization was not required of them, SP continued to maintain elevated elbow flexor and extensor activation regardless of prior perturbation or relaxation.

We next sought to determine the extent to which participants could coordinate the amount of flexor and extensor muscle activity during flexion. Thus, we used INT-RT1 ANOVA to examine main and interaction effects of participant group {NI, SP+, SP-} and task type {FLX, S-FLX, S-REV, FLX-S, REV} on a measure of CoA {CoA_{Apk}} and phasic muscle activation {$DiffA_{Apk}$}. We observed no main effect of participant group [$F_{(2,17)} = 0.015$, $p = 0.986$, Fig. 4.8C] or task type [$F_{(4,68)} = 1.743$, $p = 0.151$] on CoA_{Apk}, nor did we observe an interaction effect [$F_{(8,68)} = 0.884$, $p = 0.534$]. For $DiffA_{Apk}$, we observed no main effect of group [$F_{(2,17)} = 2.335$, $p = 0.127$], consistent with all groups being able to modulate phasic muscle activity to complete a volitional flexion task. We also did not observe a significant interaction effect of participant group and task type [$F_{(8,68)} = 1.377$, $p = 0.222$]. We did observe a significant main effect of task type [$F_{(4,88)} = 7.763$, $p < 0.0005$; Fig. 4.8D] on $DiffA_{Apk}$. Specifically, presence of a prior stabilization was found to increase the amount of $DiffA_{Apk}$ (FLX ≠ S_FLX, S_REV; $p \leq 0.001$; $p \geq 0.845$ in all remaining cases), indicating that presence of prior stabilization was associated with increased phasic muscle activity compared to movements made without prior stabilization. This is consistent with using more phasic muscle activation to compensate for increased arm impedance due to stabilization-related CoA.

Relating task performance to clinical function

We used separate forward linear regression analyses to test the hypothesis that deficits of coordination between the control of limb position and limb movement correlate significantly with motor impairment and deficits of motor function after stroke as quantified by CAHAI and FM_M scores. For both analyses (function and impairment) we used the results of the preceding correlation (Table 4.2) to identify which performance

variables to include as potential contributors to function and impairment. These included $\sigma_{stabilize}$ from the S condition to account for stabilization control and v_{pk} from the FLX condition to account for movement control. We justify the choice of a single measure for movement control because ET, N_{SM}, ΔN_{SM}, and v_{pk} are all highly correlated with one another ($r \geq 0.722$, $p < 0.0005$, n = 50 in all cases). We also included as potential model variables measures of strength (τ_{max}), spasticity (MAS), mild cognitive impairment (MoCA), and sensation (AMDT). The only significant relationship observed was τ_{max} and CAHAI [standardized $\beta = 0.681$, $t = 2.633$, $p = 0.03$]. Likely due to the small and variable group, none of the measures were found to be significantly correlated to FM_M. The only variable approaching statistical significance in the FM_M regression model was weakness (τ_{max}; standardized $\beta = 0.618$, $t = 2.223$, $p = 0.057$).

DISCUSSION

Addressing our first experimental objective to quantify the extent to which stroke impairs control and coordination of limb position and movement, survivors of stroke showed impaired ability to stabilize the more-impacted arm against mechanical perturbation of the elbow joint, and made slow, segmented movements compared with neurologically intact controls in a series of tasks consisting of combinations of targeted elbow flexion movements and stabilization of the elbow against a moderate mechanical perturbation. The extent of these deficits was impacted by the presence of proprioceptive impairment: Within the group of stroke survivors, those with *intact* proprioception were better able to stabilize the arm against a perturbation, but moved more slowly and required more submovements to complete targeted elbow flexions; those with *impaired*

proprioception had greater variability when attempting to stabilize the elbow, but moved more quickly and required fewer submovements to complete targeted elbow flexions. In compound tasks requiring sequential combinations of elbow movement and stabilization, we observed that participants in all groups had greater variability during stabilization tasks immediately prior to a targeted movement (compared with stabilization alone; participants were reminded of the upcoming task prior to the start of each trial), though survivors of stroke had a significantly greater increase in variability than did neurologically intact controls suggesting greater co-articulation of control actions after stroke. We did not observe a similar co-articulation effect on the number of submovements in targeted flexion tasks (i.e., the number of submovements to complete a targeted movement after stabilization was not significantly different from the number of submovements required to complete the task in isolation). It is not clear from this experiment if this observation is related to the nature of control (i.e., stabilization vs. movement) or the order of execution (anticipation of the next action or carryover from the prior action). Additionally, we observed that survivors of stroke never fully relaxed the muscles of the arm, while neurologically intact controls relaxed the muscles between trials and showed different levels of background activity based on very recent history (i.e., greater CoA immediately after stabilization, less CoA after resting), survivors of stroke showed consistent levels of CoA regardless of their immediate history.

Analyses addressing our second experimental objective found that within our cohort of stoke survivors, only a measure of elbow joint weakness contributed significantly to scores on the Chedoke Arm and Hand Activities Inventory. While weakness was the most important factor in accounting for variability in Fugl-Meyer

scores of motor impairment in the more-impacted arm, it did not achieve statistical significance. These results confirm and extend prior findings that arm positional stabilization control actions and movement control actions can be differentially impacted by stroke (Scheidt and Stoeckmann 2007); whereas deficits of arm proprioception compromise stabilization of the arm, the presence of clinically-intact proprioception may actually interfere with control of movement after stroke.

Non-task-relevant residual muscle elevation observed in SP may contribute to slowness of movement

Whereas neurologically intact controls reduced CoA when resting before movements without prior stabilization, survivors of stroke maintained the same elevated CoA prior to flexion for all trial types. In addition, both stroke survivor groups demonstrated a flexion bias in resting arm position prior to movement without visual feedback of hand position (FLX, REV, FLX_S conditions, Fig. 4.9B). Together, these behaviors can be explained by the SP groups' flexors retaining residual activity and the extensors activating to balance the flexors to keep the arm still. This is consistent with our prior findings with the same group of stroke survivors performing an isometric torque tracking task at the elbow. Specifically, while SP were able to modulate difference activity to create isometric flexion and extension torques, when SP attempted to perform an extension torque from rest, activation in the flexors *increased* requiring even greater levels of activation in the extensors to complete the task (see Chapter 3).

Similar deficits in selectively activating individual muscles was observed by Kamper and Rymer (2001) who examined isometric torque production, isokinetic extension, and unloaded extension of the metacarpophalangeal (MCP) joints of the more-

impacted limb. Kamper and Rymer observed impairments in selective activation of the extensors and inappropriate coupling of flexors and extensors. A later experiment by Kamper and colleagues (2003) in which survivors of stroke performed voluntary and mechanically imposed extension at the more-impacted MCP joints both before and after a nerve block was administered to the more-impacted finger flexors led to the observation that over the course of successive voluntary *extension* movements of the MCP joint, *flexor activity increased* with successive trials. In addition, flexor activity was observed to continue after voluntarily extending at the MCP joint, leading to production of a constant, steady-state torque after movement termination. Canning and colleagues asked survivors of stroke to perform an elbow flexion/extension tracking task with the arm supported against gravity to measure elbow flexor/extensor coordination while minimizing force requirements for successful task performance (2000). They found that excessive muscle activation and the inability to appropriately coordinate flexors and extensors were the critical factors in separating those who performed well and those who performed poorly on this tracking task (Canning et al. 2000).

Force exerted due to even low levels of residual activation in the elbow extensors would act as a brake on the elbow flexion movement. Increased activation of the elbow flexors would be required to overcome these opposing forces. All participants were able to modulate phasic muscle activity (DiffA) during the movement, which is necessary for movement (Fig. 4.9D). Furthermore, all groups increased the amount of positive DiffA (i.e., increased flexor activity relative to amount of concurrent extensor activity) in flexion movements occurring after stabilization compared with the flexion task alone. The increase in DiffA after limb stabilization is likely compensatory behavior due to

increased limb impedance (i.e., increased resistance due to extensor forces) from CoA (Scheidt et al., 2011).

Increased CoA of elbow flexors and extensors could lead to slowness of movement. In order to produce elbow flexion, the forces exerted by the shortening elbow flexors must exceed the forces exerted by the lengthening elbow extensors. The length-tension and joint angle-torque production characteristics of muscle do not favor the elbow flexors in this scenario: the maximal possible force the shortening flexors can create decreases as the arm flexes and the muscle shortens, while the maximal possible force of the lengthening extensors simultaneously increases (cf. Gray et al. 2012). Additionally, the force-velocity characteristics of muscle require slow movement when attempting to overcome large forces. When shortening, the force production capacity of muscle decreases as velocity of the movement increases; when muscle is lengthening, the force production capacity increases as the velocity increases (Lieber 2002). If the elbow extensor is tonically active, it can generally create greater and greater forces as it is stretched, while the elbow flexors produce lesser and lesser forces as they are shortened. Slowing the velocity of the elbow flexion would be a viable strategy to increase the force production capacity of the elbow flexors while reducing the force production capacity of the elbow extensors.

Role of proprioception in control of movement and stabilization

As previously described, movement and stabilization of the arm are guided by distinct control actions (Humphrey and Reed 1983, Sainburg et al. 1999, Scheidt and Ghez 2007). Sainburg and colleagues propose a three-stage control system in which

simple movements of the arm consist of these control actions implemented in an overlapping sequence (Sainburg et al. 1999). In this paradigm, movement is initiated by a feedforward, anticipatory control action. During movement, an online controller is responsible for error correction. Finally, a positional control action is responsible for terminating movement and stabilizing the limb (Sainburg et al. 1999).

Later studies of trajectory and positional control actions indicate that these two control actions are controlled by distinct neural circuits. Scheidt and Ghez (2007) designed experiments to isolate anticipatory and positional control actions by requesting participants move quickly enough that online error correction would not ocurr in a given movement. They further isolated movement control actions by creating "slicing" tasks of two sequential, targeted point-to-point movements in which the participant reached for the target and immediately reversed direction after transiently acquiring the target. Using this methodology, they gave participants rotated visual feedback of the final hand position in reaching (anticipatory/positional) or the reversal point in slicing (anticipatory/anticipatory/positional) tasks. Learned visuomotor rotation of the first movement target did not generalize between the two tasks, suggesting that positional control actions and movement control actions are controlled by different mechanisms (Scheidt and Ghez, 2007). A further study by Ghez and colleagues (2007) supported this finding and established that final hand position in the reach task was calculated in a head- or shoulder-centered coordinate frame, while the movement task was calculated in a hand-centered coordinate frame. Together, this evidence supports the existence of distinct neural control of movement and stabilizing the limb.

Impact of proprioceptive impairment on stabilization

The results of this study demonstrate differentially impacted movement and positional control after stroke, and find that proprioceptive impairments largely explain these impacts. Across several multi-joint, point-to-point reaching experiments of right-handed, neurologically-intact participants, Sainburg and colleagues have developed a theory that lateral differences in the brain have optimized the dominant (right hand) and non-dominant (left hand) upper extremity for executing dynamic and positional control actions, respectively (Sainburg 2002; Bagesteiro and Sainburg 2002, 2003; Sainburg and Schaefer 2004), though there is no proposed mechanism for this difference. In this framework, the left hemisphere of the brain (and right hand) is better at controlling movement, while the right hemisphere (and left hand) is better at controlling position.

Schaefer and colleagues tested properties of movement and stabilization in the less-impacted arm to test the hypothesis of laterality in these control mechanisms. Survivors of stroke performed multi-joint, point-to-point reaching experiments using the less-impacted arm. These studies found that stroke differentially impairs visuomotor adaptation of these control actions (Schaefer et al. 2009) and online error corrections in point-to-point reaching tasks (Schaefer et al. 2011). The observed impairments depended on which hemisphere was predominantly affected by stroke: Those with injury to the right hemisphere (which controls the left arm and hand) showed impairments in control of position, while those with injury to the left hemisphere (which controls the right arm and hand) showed impairments in control of movement regardless of whether the right or left hand was tested. These results are consistent with the dominant/non-dominant brain

laterality (as tested in exclusively right-handed populations) as well as differential impact of stroke on position /movement control actions.

Mani and colleagues (2013) tested the laterality hypothesis in the more-impacted arm of stroke survivors. In another multi-joint, point-to-point reaching experiment, a similar result was found. Damage to the left hemisphere was associated with degradation of movement control, and damage to the right hemisphere was associated with degradation of movement termination (Mani et al. 2013).

Results of the current study suggest that the differences observed in impairments of movement and stabilization after stroke can also be related to proprioception in addition to laterality. Reported lesion side, consistent with clinical presentation of motor symptoms, was evenly split within both proprioception groups (SP+: 3 right-, 3 left-hemisphere stroke; SP-: 2 right-, 2 left-hemisphere stroke, Table 4.1). A larger sample would be required to confirm this supposition.

We cannot evaluate potential effects of proprioceptive deficits in Schaefer and colleagues' (2009, 2011) or Mani and colleagues' (2013) work, as no measure of proprioceptive impairment was reported in the studies. However, Kenzie and colleagues (2016) reported that out of 142 sub-acute ischemic stroke survivors, 76% of those with right-hemisphere lesions showed deficits in proprioception, while only 37% of those with left-hemisphere lesions showed similar deficits. If right-hemisphere lesions are more likely to cause proprioceptive deficits, and the right hemisphere is associated with position control (Sainburg 2002; Bagesteiro and Sainburg 2002, 2003; Sainburg and Schaefer 2004), the observed deficits in position control after right-hemisphere damage (Schaefer et al. 2009, Schaefer et al. 2011, Mani et al. 2013) are consistent with our

present observation that stroke-related deficits in proprioception are related to degraded control of limb position when stabilizing against a perturbation. Stroke-related deficits in position control at the end of reaching movements were also found in survivors of stroke with impaired proprioception (Scheidt and Stoeckmann 2007). Thus, impairment of proprioception likely contributes to degraded control of limb position after stroke.

Impact of proprioceptive impairment on movement

In an intact sensorimotor system, short movements can be made with a single submovement while long-duration movements are generally composed of a series of proprioception-driven corrective submovements. Submovements are generally characterized by multiphasic peaks in a velocity trace rather than a single, bell-shaped curve (Fishbach et al. 2006, Cirstea and Levin 2000, etc.). These phasic peaks are the result of feedback control interrupting an ongoing movement (Keller et al. 1996, Xu-Wilson et al. 2011) in order to correct for position errors (Vince 1948, Schaefer et al. 2009). The fact that targeted point-to-point reaching movements are computed in a hand-centered, rather than eye-centered, coordinate frame (Ghez et al. 2007) suggests that the feedback mechanism may be intrinsic to the limb, i.e., proprioception, rather than visual feedback. In neurologically-intact participants performing continuous tracking, these interruptions happen approximately every 400 to 500 ms (Craik 1947), which is consistent with observed performance in this experiment (Fig. 4.7A, B). However, in patients without proprioception due to large-fiber sensory neuropathy, single-peak, bell-shaped velocity profiles have been recorded over time courses of 1000 ms or more (Gordon et al. 1995).

Interestingly, we see that survivors of stroke with *intact* proprioception took longer to complete the flexion movement, required more submovements, had lower peak velocity during their first submovement, and greater target undershoot error at the end of the first submovement than did SP with *impaired* proprioception. These submovement, feedback interruptions do not appear in NI participants, who can appropriately coordinate multiple control actions and quickly execute the targeted point-to-point movement. It is possible that the smaller number of submovements observed in stroke survivors with *impaired* proprioception is due to either the motor system disregarding proprioceptive information that is known to be unreliable, or a simple lack of the proprioceptive signal that would interrupt a movement. For stroke survivors with *intact* proprioceptive signals, however, increases in the number of submovements may indicate a problem with effectively integrating proprioceptive information during the movement, or due to increased opportunity for corrective submovements due to longer movement durations.

Some support for the supposition that better integration of sensory and motor signals decreases the number of submovements required to make a targeted point-to-point movement comes from Rohrer and colleagues (2002, 2004), who used the number and amplitude of submovements made during multi-joint reaching tasks using more-impacted arms of acute- and chronic-stage stroke survivors as a means of tracking recovery. Rohrer and colleagues observed that as patients progress through stroke recovery (as quantified by time elapsed since stroke and improvement of FM_M scores, which indicates improvement in integrated control and coordination of limb segments), the number of submovements required to complete a point-to-point reaching task declines, and the individual submovements tend to have greater overlap (Rohrer et al. 2002, Rohrer et al.

2004). It is possible that as neural and motor recovery progresses after stroke, stroke survivors may become better able to integrate incoming sensory signals into their motor plan and execution. Unfortunately, Rohrer and colleagues did not report proprioceptive status of the participants in their studies (2002, 2004), so we cannot know if improved performance (measured by decreases in number of submovements) was more common in those with impaired proprioception.

Coordination of control actions after stroke: SP, NI showed similar patterns of co-articulation in sequential control actions

Co-articulation is a phenomenon first described in studies of the production of language (see Thomassen and Schomaker 1986 for a review). It describes the phenomenon wherein two actions influence one another in either an anticipatory (where one action changes to accommodate an upcoming action), or carryover (where one action is changed due to the prior action) manner. The model of co-articulation depends on the assumption that speech consists of discrete phonological units and that the properties of a given unit will vary based on the properties of adjacent units (Kuhnert and Nolan 1999). A similar phenomenon has been observed in handwriting, where it has been observed that hand position and velocity during letter formation are both affected by adjacent letters, with larger impacts resulting from anticipation than carryover (Thomassen and Schomaker 1986). Sosnik and colleagues (2004) examined co-articulation in targeted, multi-joint point-to-point reaching movements in which participants repeatedly traced a circuit between four targets. They found that with practice, participants created a new curved path that, while longer than the sum of path-lengths between the targets, allowed

participants to complete the task more quickly without sacrificing accuracy of target acquisition.

In the current results, we observed a significant anticipatory main effect of upcoming movement on stabilization variability (Fig. 4.6). We also observed a significant carryover main effect of prior stabilization on number of submovements needed to complete the flexion task (Fig. 4.7B). These interactions were observed in all groups, despite the broad range of impairment in the SP group. These findings indicate that there is co-articulation between position and movement control actions in all of the participants who performed this experiment. We further quantified the impact of anticipated movement on stabilization variability using $\Delta\sigma_{stabilize}$, the difference in position variability during stabilization against perturbation with and without a planned movement following. We observed that SP showed a greater increase in $\Delta\sigma_{stabilize}$ than did NI (Fig. 4.8A). This indicates that stroke amplified the anticipatory co-articulation effect of upcoming movement on stabilization variability. We further quantified the impact of carryover of stabilization on a flexion movement using the variable ΔN_{SM}, the difference in the number of submovements required to complete the flexion task with and without a prior stabilization (Fig. 4.8B). No significant difference was observed in ΔN_{SM} between groups, indicating that stroke did not impact carryover co-articulation of flexion movement and prior stabilization.

In addition to the kinematic coupling of stabilization and movement, we also observed a carryover impact of stabilization on muscle activity. Specifically, stabilization prior to flexion was associated with greater levels of positive difference activity (net flexor activity) during the following flexion movement (Fig. 4.9D). This was likely to

compensate for increased limb impedance due to residual co-activity observed after the stabilization had ended. Interestingly, this indicates that despite observed differences in residual muscle activation prior to movement (Fig. 4.9B), SP and NI demonstrate similar coordination of phasic muscle control.

Limitations of study

Our study design was limited to examining flexion and stabilization about the elbow. This choice was made to attempt to isolate the coordination of position and movement control actions with as little interference as possible from the coordination of multi-joint planning and execution. This may, however, limit the study's direct applicability to whole-limb or bimanual tasks, as evidenced by the inability of the experiment outcome measures to account for variability in measured bimanual function and impairment in the more-impacted limb as a whole (CAHAI and FM_M scores, respectively).

Additionally, we had originally planned to examine the extent to which terminal condition of the flexion movement (e.g., reverse to extend, stop moving, stabilize against a perturbation) impacted performance on the movement itself. We chose not to complete these analyses given the large number of submovements used by SP to complete the flexion task making it impossible to confidently relate the first flexion submovement to the anticipated termination state of the flexion task as a whole. Thus, we restricted our analyses to our baseline control actions (S and FLX) and conditions with initial stabilization and the flexion movement immediately following (S-FLX, S-REV).

Conclusions

The present study supports previous findings that stroke differentially impairs control of targeted point-to-point movement and stabilization of the arm. Additionally, this study supports the supposition that survivors of stroke may have greater impairments in the control of limb stabilization, while survivors of stroke with intact proprioception may have greater deficits in moving the limb. This study also supports the presence of both anticipatory and carryover co-articulation of sequential stabilization and movement motor commands. Furthermore, we observed that survivors of stroke were unable to reduce the amount of co-activation present in elbow flexor/extensor pairs even when there was no functional reason for activity, whereas neurologically intact controls relaxed the elbow muscles when they were not required for movement or stabilization of the arm. Finally, weakness was found to relate to decreased motor function and increased motor impairment as measured by clinical evaluations.

CHAPTER 5: CONTRIBUTIONS OF COORDINATION TO FUNCTIONAL OUTCOMES AFTER STROKE

Weakness is known to contribute to motor impairment and decreased motor function after stroke. However, we suspect that the ability to coordinate the magnitude and timing of activation in opposing muscles, and the ability to coordinate sequential stabilization and movement control actions, also contribute to functional outcomes. In this study, we quantified the extent to which broad measures of function and impairment of the more-impacted arm after stroke were explained by specific stroke-related deficits. These measures include deficits of motor control, somatosensation, cognition, coordination of agonist/antagonist muscle pairs, and coordination of sequential stabilization and movement control actions. We found that after stroke, weakness accounted for a significant amount of variability in upper extremity motor function as quantified by the Chedoke Arm and Hand Activity Inventory. We further found that the rate at which participants could reduce measured torque after creating elbow flexion torque, as well as their ability to reduce the amount of muscle activation present after torque production, accounted for a significant amount of variance in upper extremity motor impairments as quantified by the upper extremity motor portion of the Fugl-Meyer Assessment. These results suggest that coordination of the magnitude of activation in agonist/antagonist muscle pairs – and not just pure strength – is an important factor in motor impairment and function after stroke.

Introduction

Reaching is an important functional behavior as it allows one to interact with the environment. Successful point-to-point reaching requires sufficient strength to move the arm as well as adequate coordination to orchestrate multiple joints in time and space. Underlying strength and joint-level coordination is the ability to coordinate agonist/antagonist muscle pairs, and the ability to successfully coordinate sequential stabilization and movement control actions. Approximately half of stroke survivors experience persistent motor deficits (Roger et al. 2012) which can include limitations in point-to-point reaching. Deficits in point-to-point reaching can negatively impact quality of life and the ability to perform activities of daily living.

Limitations in torque production after stroke include weakness and slowness in development and termination of torques about a joint in the more-impacted arm (McCrea et al. 2003, Canning et al. 2000). This slowness is related to delays in initiating and terminating muscle contractions in the more-impacted arm (Chae et al. 2002). The results of the Chapter 3 study support the negative impact of weakness on function that has been previously reported (Chae et al. 2002, Harris and Eng 2007, Kamper et al. 2006). These findings also suggest that the ability to coordinate activation in agonist/antagonist muscle pairs is an important contributor to function, above and beyond simple weakness.

In Chapter 3, survivors of stroke (SP) and neurologically intact (NI) participants created and ceased cued flexion and extension torques at the elbow using either the more-impacted arm (SP) or the dominant arm (NI). We found that compared with NI, SP were weaker, took longer to create and cease torque production, and were more variable in achieving and holding a targeted torque. We also observed that both SP and NI could

modulate their muscle activity to some extent to produce torques, but SP consistently had higher levels of co-activation than did NI. Forward regression analysis of the SP data indicated that weakness, the maximal rate at which participants could reduce torque, and the ability to coordinate agonist/antagonist muscle activity when reducing torques accounted for significant amounts of variability in motor function after stroke as measured by the Chedoke Arm and Hand Activities Inventory.

Targeted, point-to point reaching movements consist of a series of sequential, partially-overlapping control actions (Feldman 1980a, b, Humphry and Reed 1983). These actions include a feedforward control action for initiating movement, a proprioception-dominant online movement correction control action, and a separate, positional control action that stabilizes the arm at the end of movement (Sainburg et al. 1999, Scheidt and Ghez 2007, Ghez et al. 2007). There is mounting evidence that these control actions are differentially impaired by stroke. Some groups have observed that stroke laterality accounts for these differences (Schaefer et al. 2009, Mani et al. 2013), while others have observed that proprioceptive deficits may account for observed differences (Scheidt and Stoeckmann 2007).

In Chapter 4, SP and NI performed a series of one-joint elbow tasks that combined stabilization against a perturbation and targeted, point-to-point movement of the elbow in different variations to examine impact of stroke on performance of individual control actions and the coordination of sequential control actions. We found that performance in stabilization and movement control actions was impaired in SP compared to NI. However, within the SP group, our result supports the view that proprioceptive impairments after stroke were associated with differential impairment of

limb stabilization and limb movement. Specifically, participants with *impaired* proprioception had higher variability when stabilizing, but less movement segmentation than SP with *intact* proprioception. A recent finding from Kinzie and colleagues (2016) suggests that proprioception may be lateralized in the brain. The laterality reported in this study suggests that proprioceptive impairments are consistent with the lateral explanation of differential control action impairment. When forward multiple regression was applied to performance and coordination measures of sequential control actions and agonist/antagonist muscle pairs, the only variable found to significantly correlate with function was weakness. This suggests that the one-joint elbow task may be limited in its applicability to functional behaviors.

In this chapter, we review behavioral and electromyographic performance of nine survivors of stroke who performed a series of isometric torque generation and cessation tasks (Chapter 3), as well as a series of stabilization and movement tasks (Chapter 4), and a series of clinical and research evaluations of function and impairments. Our final objective was to quantify the extent to which broad measures of function and impairment in the more-impacted arm after stroke are related to specific, stroke-related deficits. To achieve this objective, we use correlation analyses and multiple forward regression analyses to relate individual impairments, performance and agonist/antagonist muscle coordination during torque production, and performance and agonist/antagonist muscle coordination of movement and stabilization actions with broad measures of upper extremity motor function and impairment.

Background

Participant Characteristics

Of the participants who performed the experiments in Chapters 3 and 4, nine survivors of stroke were included in these analyses. None of the included participants were receiving botulinum toxin injections at the time of the study. S103, S108, and S112 were receiving botulinum toxin injections and thus were excluded (see Appendix 1). Additionally, S111 was excluded due to missing data caused by failure of a ground electrode that corrupted the electromyographic (EMG) signals during the Aim 2 experiment (see Chapter 4).

Upper extremity motor function was assessed using the 13-item Chedoke Arm and Hand Activities Inventory which tests participants on a series of bimanual activities of daily living. Performance in each task is scored on a scale of 1 to 7 with a score of 1 indicating that the participant could not perform the task and a score of 7 indicating that the more-impacted arm participated fully and efficiently in the bimanual task. Overall scores for CAHAI can range from 13 to 91 (see Table 5.1). Upper extremity motor impairment was assessed using the Fugl-Meyer Assessment of Sensorimotor Recovery After Stroke (FMA, Fugl-Meyer et al. 1975). The upper-extremity motor portion of the FMA (FM_M) tests the more-impacted arm for reflex activity, volitional movement (within motor synergy patterns, in mixed motor synergy patterns, and out of motor synergy patterns), wrist function, finger function, and intersegmental coordination. The FM_M is rated on a scale of 0 to 66. A score of 0 indicates a complete lack of reflexes and

volitional movement in the more-impacted arm whereas a score of 66 indicates intact reflexes, arm, and grasp movements.

Table 5.1: Participant characteristics.

ID	Age	Sex	Test Hand	Dom. Hand	τ_{max} (Nm)	FM_M	CAHAI	FM_P	MAS	MoCA	Years since stroke	Lesion Type	Lesion Location
101‡	57	M	L	R	17.3	27	18	1	1.5	27	12	I	R: Midbrain
102‡	59	M	R	R	27.9	20	24	6	4	26†	7	I	L: MCA, BG, Insular Cortex
104‡	52	M	R	R	8.8	21	23	6	3.5	23†	13	**	L: **
106‡	64	F	R	R	12.5	45	32	2	2	14†	24	**	L: **
107‡	61	M	R	R	13.0	27	15	1	2.5	10†	12	I	L: MCA Distribution
110	62	M	L	R	25.6	41	63	6	4.5	23	7	I	R: BG & Caudate
113	63	F	L	R	24.8	37	52	3	3.5	22	10	**	R: **
114	64	M	L	R	35.8	66	90	6	0	24	7	I	R: Multi-focus Periventricular White Matter
115	70	F	L	L	16.6	32	30	6	1.5	22	13	H	R: **

ID: Participant identification number, ‡: expressive aphasia, Dom: dominant hand. R: Right, L: Left. τ_{max}: average maximal torque production. FMM: Upper extremity motor portion of Fugl-Meyer Assessment, CAHAI: Chedoke Arm and Hand Activities Inventory, FMP: Proprioception subsection of upper extremity sensory Fugl-Meyer Assessment, MAS: Modified Ashworth Scale, MoCA: Montreal Cognitive Assessment. MCA: Middle cerebral artery, BG: Basal ganglia; ** Data not available.

Clinical and Research Measures of specific, stroke-related impairments

Three measures were used to evaluate somatosensation: we administered the sensory portion of the FMA which includes a coarse test of proprioceptive acuity (FM_P) and light touch (FM_{LT}, Fugl-Meyer et al. 1975), as well as a robotic measure of kinesthetic detection threshold (AMDT, Mrotek et al. 2017). The FM_P, also referred to as the clinical "up or down?" test (DeGowin et al., 1987; Epstein et al., 2008), was used to assess overall proprioceptive discrimination at the thumb, wrist, and elbow joints. Proprioception at each joint was graded 2 (intact), 1 (impaired), or 0 (absent). Scores were summed across joints to give a total of 6 possible points. The light touch portion of the FMA (FM_{LT}) was also assessed. Sensation of light touch was judged to be intact (2), impaired (1), or absent (0) giving a possible of 4 points for FM_{LT}. An additional laboratory test of proprioceptive integrity (AMDT) was also administered. In this laboratory test, the participant's hand is attached to a 2-degree-of-freedom, planar robot and view of the hand is obstructed. Ten perturbation trials (5 ascending, 0 to 2 N; 5 descending, 2 to 0 N) are conducted. The participant reports whether they perceive that the hand is being perturbed, and the experimenter slowly adjusts the level of perturbation until the perception state changes from "no" to "yes" (ascending), or "yes" to "no" (descending). Scores reported from this measure are a statistical likelihood that the participant has intact proprioception based on comparison with a set of neurologically-intact controls. This measure has been described previously (Mrotek at al. 2017).

Strength at the elbow (τ_{max}) was tested using an isometric maximal average elbow torque production task. Participants performed two maximal flexion and two maximal extension repetitions with the arm attached to a rigid handle and the elbow

centered over a multi-axial load cell (model 75E20A4-I125-AF, JR3, Woodland, CA). The task was repeated with the arm in three positions, thus there were a total of 6 maximal flexion and 6 maximal extension torque values. The average maximal torque value (τ_{max}) was calculated by averaging across these values.

Muscle tone of elbow flexors and extensors was evaluated using the Modified Ashworth Scale (MAS, Bohannon and Smith 1987). This scale grades flexor and extensor muscle tone about a joint on a scale of 0 to 4 where a score of 0 indicates that there is no increase in tone compared to the less-affected side, and a score of 4 indicates muscle tone so severe as to render the tested joint rigid. MAS scores for elbow flexors and extensors were averaged to obtain an overall estimate of muscle tone at the elbow.

We screened for mild cognitive impairment using the Montreal Cognitive Assessment (MoCA). This measure is designed to test visuospatial/executive function, naming, attention, language, abstraction, delayed recall, and orientation (MoCA, Nasreddine 2005). Scores for the MoCA range from 0 to 30 with scores ≥26 considered normal. Due to the verbal nature of many responses, MoCA scores can be confounded by aphasia (participants with aphasia are noted in Table 5.1 by the ‡).

Post-stroke Coordination of Agonist/Antagonist Muscle Pairs in Isometric Torque Production

On the second day of experimentation (Chapter 3), participants performed isometric step-torque tracking tasks with the arm affixed to a rigid handle and the elbow centered over a multi-axial load cell (Fig. 5.1A, model 75E20A4-I125-AF, JR3, Woodland, CA). Participants viewed a screen with a target trace and a measured torque trace scrolling from right to left at a rate of 2.5 cm per second (Fig. 5.1B). Participants

created or reduced elbow flexion and extension torques with the arm attached to a fixed handle to track the torque target. In one condition, the target alternated between relaxation and 20% τ_{max} in the flexion direction (Fig. 5.1C). In a second condition, participants tracked targets alternating between relaxation and 20% τ_{max} in the extension direction (Fig. 5.1D). Thus, there were four transition conditions: producing flexion torque after relaxing (F_R), ceasing flexion torque production (R_F), producing extension torque (E_R), and ceasing extension torque production (R_E). Participants performed 2, 60-second trials of 20 transition and hold periods of each task type (10 in each direction) in three different joint angles (65º, 90º, and 105º elbow flexion). The inter-cue interval was pseudorandomly distributed such that transition times (2.9 ± 0.75 s; mean ± 1SD) were unpredictable, but identical across participants. Participants were instructed to "Match the elbow torque cursor to the target trace as quickly and accurately as possible."

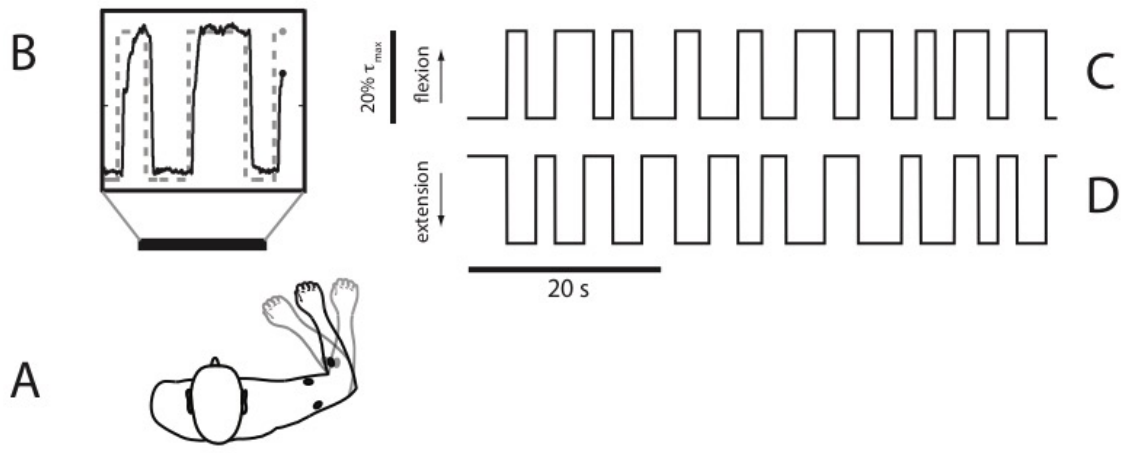

Figure 5.1: Experiment for measuring agonist/antagonist muscle coordination during an isometric step-torque tracking task. A: Participant setup. B: Monitor with torque step-tracking target and real-time elbow flexion/extension torque feedback. C: Flex/relax cue time series. D. Extend/relax cue time series. C-D alternate between 0% and 20% of average maximal torque. Note: This figure derived from Figure 3.1.

Electromyographic signals (EMG) were recorded from elbow flexors (short and long head of the biceps brachii, brachioradialis) and extensors (long and lateral heads of triceps brachii). EMG signals were zero-meaned, notch filtered at 60, 120, and 180 Hz to remove line nose, rectified, and normalized to maximal voluntary isometric contractions (MVICs). Prior to normalization, MVIC traces were processed as above, and then subjected to a 100 ms sliding average filter before determining the maximal value. One primary flexor and one primary extensor were selected as the muscle that most highly correlated with torque production during a maximal voluntary exertion task (see Chapter 3 for further detail).

Measures of the coordination of agonist/antagonist muscle activation magnitude were calculated between the selected flexor and extensor. Specifically, we estimated the amount of normalized EMG that was equal-and-opposite in the antagonist muscle pair using a measure of instantaneous muscle co-activation (CoA, Equation 5.1):

$$CoA(t) = \min\left[flexor(t), extensor(t)\right]. \qquad \text{[Eq. 5.1]}$$

The CoA measure quantifies the smallest amount of activity present in the muscle pair. We also calculated a measure of instantaneous net muscle activation called difference activity (DiffA, Equation 5.2)

$$DiffA(t) = flexor(t) - extensor(t). \qquad \text{[Eq. 5.2]}$$

DiffA(t) quantifies the instantaneous amount of phasic activation in the antagonist muscle pair beyond the level of shared activation in CoA. We used these two performance measures to quantify the instantaneous coordination between antagonist muscles spanning the elbow joint. Two, 50-ms time windows were of interest for the current analyses. Specifically, phasic muscle activation immediately prior to peak rate of change

of torque ($DiffA_{Tpeak}$), and co-activation and phasic activation starting 150 ms after torque transition ended (CoA_{Tend}, $DiffA_{Tend}$, see Chapter 3 Methods for specifics on defining transitions).

Two specific measures of stroke-related deficit were defined to describe performance during isometric torque production/cessation transitions. The first was the peak rate of change of torque ($\dot{\tau}_{peak}$, see Fig. 5.2A). Recalling Chapter 3, neurologically-intact participants tended to relax from torque production more quickly than they produced torques (cf. Fig. 3.6A). Here, however, SP tended to have similar or slower transition speeds when attempting to relax from torque production (R_F, R_E) as when producing torque (F_R, E_R). This is most marked in the difference between the rates observed producing (F_R) and reducing (R_F) flexion torque: Indeed, S114 is the only participant in this cohort who was able to relax more quickly than produce torque.

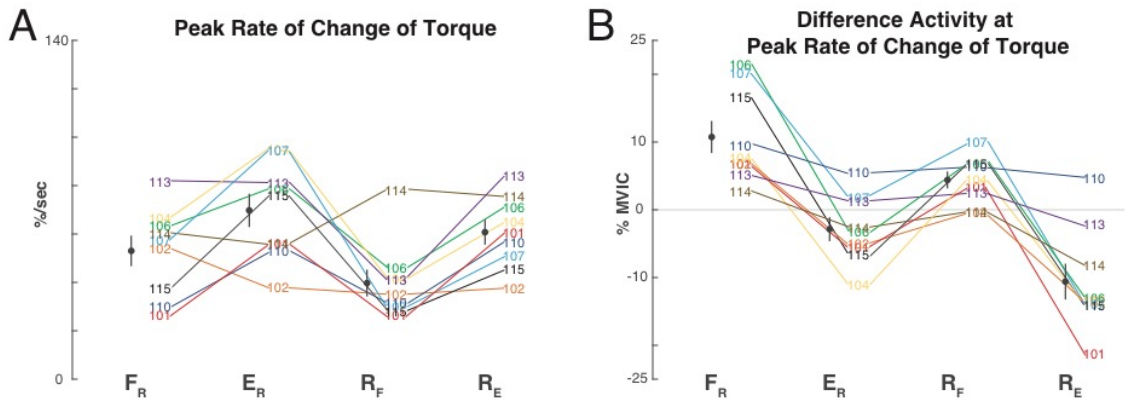

Figure 5.2: Behavior and muscle activity during isometric elbow flexion and extension torque production. Transition types include flexion after relaxation (F_R), extension after relaxation (E_R), relaxing after flexion (R_F) and relaxing after extension (R_E). Black circles indicate mean, error bars denote ± 1 S.E.M. Colored lines connect transition-type averages for each participant. A: Peak rate of change of torque. B: DiffA (muscle activation above the level of co-activation) during transition. Note that positive values of DiffA indicate predominant flexor activity, while negative values indicate predominant extensor activity.

The second measure used to describe performance during transitions was DiffA at $\dot{\tau}_{peak}$ (Fig. 5.2B). DiffA is a measure of muscle activation above and beyond the minimum amount of activity present in both muscles of the agonist/antagonist pair. When the flexor is more active than the extensor, DiffA is positive; when the extensor is more active than the flexor, DiffA is negative. All participants in this cohort had predominant flexor activity when producing flexion torque (F_R), but three of the participants still had predominant flexor activity when producing extension torque (E_R). When reducing flexion torques (R_F), participants tended to have less net flexor activity than when producing torque (F_R). When reducing extension torques (R_E), however, participants tended to have *greater* levels of extensor activity (i.e., more negative DiffA value) than when producing extension torques (E_R). This may suggest that survivors of stroke are slow to activate and deactivate muscles at the elbow, especially the extensors.

We next examined two specific measures of stroke-related deficits of elbow agonist/antagonist coordination 150 ms after the end of transition. The first measure was CoA, the minimum amount of activity present in both muscles within the time window of interest (Fig. 5.3A). Of note, participants tended to have the greatest levels of CoA when reducing extension torque, indicating that both the flexor and extensor were active (up to 10% MVIC for S104) after reducing extension torque (R_E). This high amount of muscle activation is also clearly visible in DiffA after the end of transition (Fig. 5.3B): When relaxing from extension torque production (R_E), the majority of participants show high levels of extensor activity above and beyond the baseline CoA (which indicates the minimum amount of muscle activation present in the flexor/extensor pair) that is

subtracted from the measure. Indeed, S101 has nearly 30% MVIC activation of the extensor when reducing extensor torque.

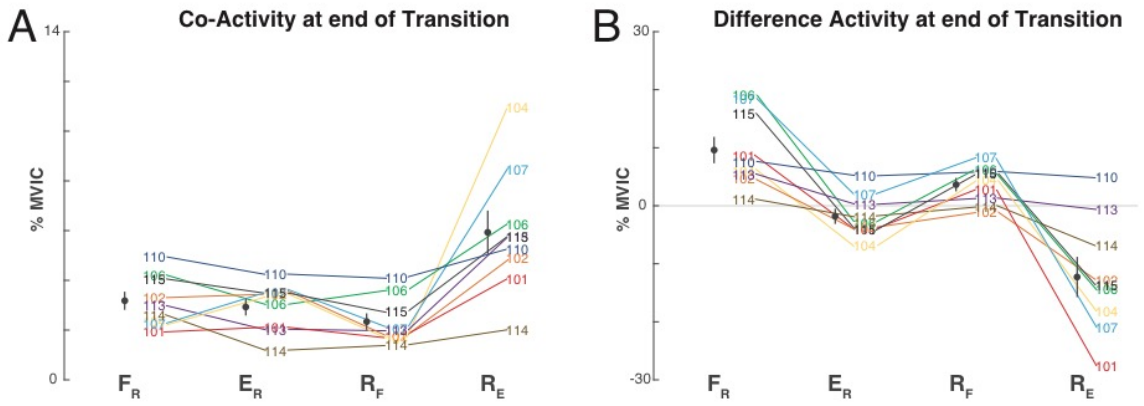

Figure 5.3: Agonist/antagonist muscle coordination 150 ms after end of transition. Transition types include flexion after relaxation (F_R), extension after relaxation (E_R), relaxing after flexion (R_F) and relaxing after extension (R_E). Black circles indicate mean, error bars denote ± 1 S.E.M. Colored lines connect transition-type averages for each participant. A: CoA after transition completion. B: DiffA after transition completion. Note that positive values of DiffA indicate predominant flexor activity, while negative values indicate predominant extensor activity

Post-stroke Coordination of Sequential Movement and Stabilization Control Actions

On the third day of experimentation, participants performed one-joint elbow tasks that combined stabilization and point-to-point elbow flexion and extension movements. The more affected hand was fixed, palm down, to a rigid handle (Fig. 5.4A). The elbow was aligned with the center of rotation of a motor that could apply force to the handle and resolve handle position (D061A DC, Kollmorgen, Radford, VA), and a multi-axis load cell to measure forces and torques applied to the handle (67M25A-I40-A-200N12; JR3, Woodland, CA). View of the arm was obstructed with an opaque screen. Participants viewed a computer monitor (Fig. 5.4B) that displayed visual cues and performance feedback related to each trial type as described below. Here, we evaluate performance in

four of the tasks performed: *Stabilizing* against a perturbation (S, Fig. 5.4C), a targeted, point-to-point elbow *flexion* movement (FLX, Fig. 5.4D), and a combination of stabilization against a perturbation and flexion, *stabilize*, *flex* (S-FLX, Fig. 5.4E), and a sequential combination of *stabilize*, *flex, extend* (i.e., a reversal; S-REV, Fig. 5.4F; see Chapter 4 Methods for specific details on task and calculation of outcome measures).

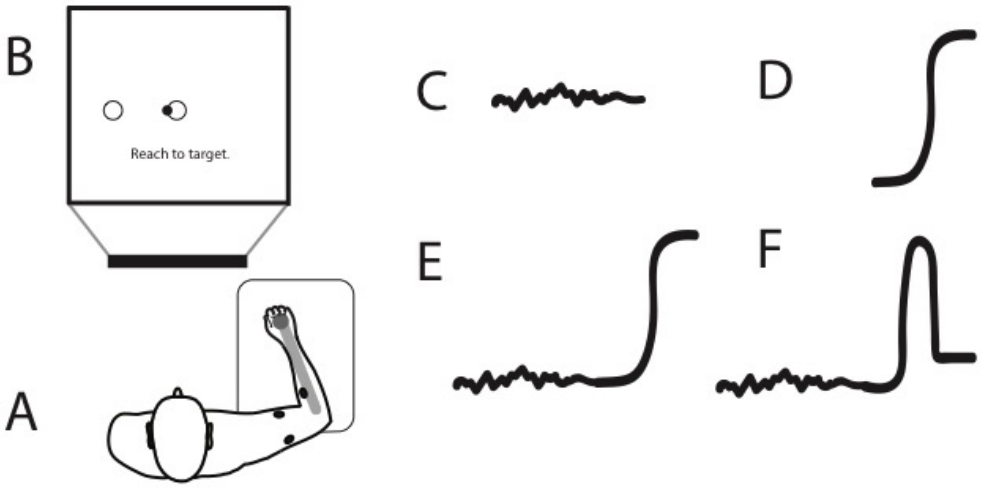

Figure 5.4: Experimental setup and tasks. A: Participant setup (opaque screen not shown); B: Participant viewed task instructions, target locations, and performance feedback on a visual display; C-F: Cartoon depictions trajectories of task types over time, C: Stabilze (S); D: Flex (FLX); E: Stabilize, flex (S-FLX); F: Stabilize, flex, extend (S-REV). Note: This figure derived from Figure 4.1.

Surface electromyograms (EMG) were recorded from elbow flexors and extensors, as previously described above. One flexor and one extensor were chosen for analysis. The muscle chosen for each group was the one with the highest signal-to-noise ratio of the processed EMG from the MVIC and relax trials. EMG processing and calculation of instantaneous measures of agonist/antagonist coordination were identical to those described above.

From this study, we focused on specific measures of agonist/antagonist coordination in muscle and coordination of sequential control actions. The measures of muscle agonist/antagonist coordination included co-activity during the last 50 ms of stabilization (CoA_S) and difference activity during FLX, just prior to peak acceleration of the first flexion submovement, ($DiffA_{Apk}$). We also used two measures of coordination between sequential stabilization and movement control actions. The first of these measures, $\Delta\sigma_{stabilize}$, characterizes anticipatory co-articulation of anticipated flexion on stabilization; this measure was calculated as the difference in the amount of variability observed during stabilization against a perturbation when a movement was anticipated, and when one was not. The second measure, ΔN_{SM}, characterizes carryover co-articulation of prior stabilization on the flexion movement action; this measure was calculated as the difference between the number of submovements required to complete the flexion task after stabilization, and the number of submovements required to complete the flexion task alone.

Two of these measures relate to stabilization of the elbow against a perturbation: $\Delta\sigma_{stabilize}$ and CoA_S (Fig. 5.5, left and right, respectively). Interestingly the four participants with the least amount of anticipatory co-articulation (S114, S104, S102, S101) also had the lowest levels of CoA during stabilization (S).

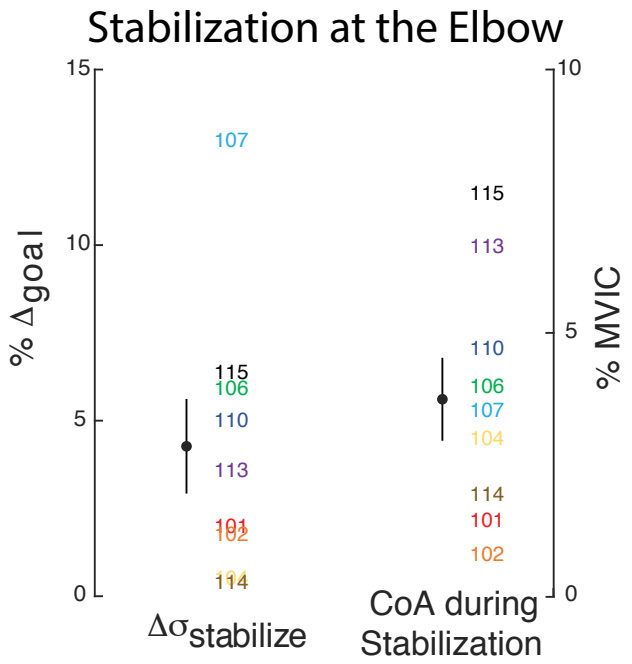

Figure 5.5: Stabilization about the more-impacted elbow. Left: Change in position variability between stabilize condition alone (S) and in conditions with upcoming movement (S-FLX, S-REV). Right: Co-activity during the last 50 ms of stabilization (S).

The other two specific measures from this experiment relate to movement of the arm. The first measure, ΔN_{SM} (Fig. 5.6, left), quantifies anticipatory co-articulation, in this case the impact of prior stabilization on the number of submovements required to successfully complete a point-to-point elbow flexion task. While many of the participants in this analysis showed modest anticipatory co-articulation, S114, S110, and S115 all demonstrated a markedly larger increase in the number of submovements required to complete the task after having previously stabilized the arm against a perturbation. The second movement measure was $DiffA_{Apk}$ (Fig. 5.6, right), which quantifies the net muscle activation (above the shared CoA baseline) with positive values indicating predominant flexor activation and negative values indicating predominant extensor activation. While most of the participants demonstrated positive DiffA values, which would be expected during a flexion movement, S104, S102 and S110 all demonstrated negative DiffA values

indicating that they had predominant extensor activation despite the fact that they were flexing the elbow.

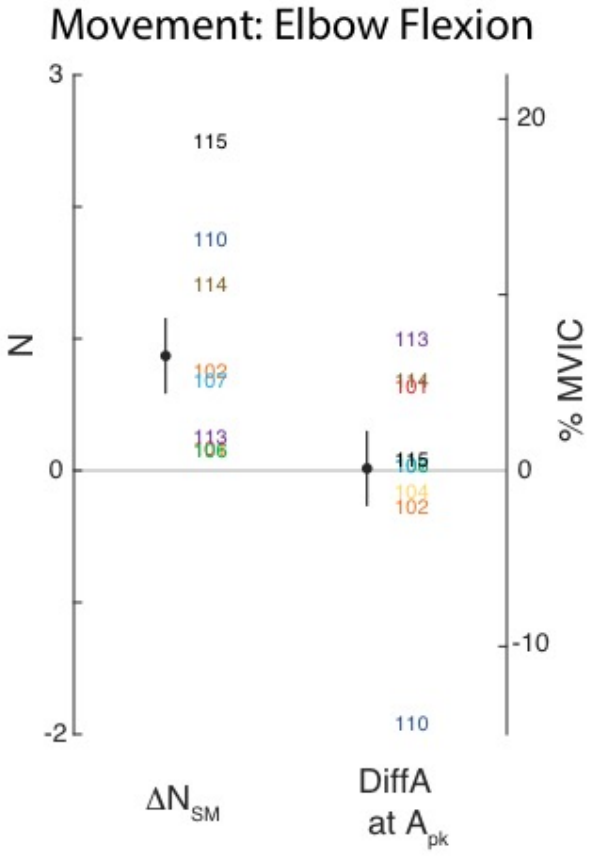

Figure 5.6: Movement of the more-impacted elbow. Left: Change in the number of submovements required to complete targeted point-to-point flexion between isolated flexion task (FLX) and compound tasks with prior stabilization (S-FLX, S-REV). Right: Difference activity at the first acceleration peak of elbow flexion (FLX). Note that positive DiffA values indicate predominant flexor activity and that negative DiffA values indicate predominant extensor activity.

Methods

We used a combination of correlation and multiple forward regression analyses in order to quantify the extent to which broad measures of function and impairment in the more-impacted arm after stroke are impacted by specific, stroke-related deficits. We first used correlation analysis to quantify relationships between upper extremity measures of

function and impairment after stroke, measures of specific deficits, coordination of agonist/antagonist muscle pairs, and coordination (or co-articulation) between sequential control actions. To this end, we correlated {CAHAI, FMM} with specific deficit measures {FM_P, FM_{LT} AMDT, τ_{max}, MAS, MoCA}, as well as the speed of isometric torque transitions $\{\dot{\tau}_{peak}\}$, three measures of isometric muscle coordination {$DiffA_{Tpeak}$, CoA_{Tend}, $DiffA_{Tend}$}, two measures of coordination of sequential control actions {$\Delta\sigma_{stabilize}$, ΔN_{SM}}, one measure of muscular coordination during stabilization (S) {CoA_S}, and a final measure of muscular coordination during targeted elbow flexion (FLX) movement {$DiffA_{Apk}$}. Isometric measures included values for each of the four transition types $\{F_R, R_F, E_R, R_E\}$.

Next, we sought to quantify the extent to which specific deficits of sensation, strength, muscle tone, cognition, speed, coordination of agonist/antagonist muscle pairs, and coordination of sequential stabilization and movement control actions could account for differences in upper extremity motor function (measured by CAHAI) and impairment (FM_M). We performed two forward regression analyses to model {CAHAI, FM_M}, using specific deficit measures from clinical and research evaluations: {FM_P, FM_{LT} AMDT, τ_{max}, MAS, MoCA, $\dot{\tau}_{peak}$, $DiffA_{Tpeak}$, CoA_{Tend}, $DiffA_{Tend}$, CoA_S, $DiffA_{Apk}$, $\Delta\sigma_{stabilize}$, ΔN_{SM}}. Multiple forward regression analysis allows these specific deficit measures to compete with one another to create a model that explains the variance observed in CAHAI and FM_M scores amongst the population of SP. Additionally, multiple forward regression quantifies the extent to which each independent variable explains differences in the dependent variable, allowing us to achieve our objective.

Results

In this study, we first used correlation analysis to quantify the relationships among a plurality of measures of specific impairments and coordination after stroke. We then used forward regression to quantify the extent to which these specific impairments accounted for variability in measures of overall function and impairment in the more-impacted upper extremity after stroke as measured by a clinical test of bimanual tasks of daily living (CAHAI) and a clinical test of motor impairment (FM_M). These analyses allowed us to quantify the extent to which variations in broad measures of function and impairment in the more-impacted arm after stroke are accounted for by specific, stroke-related deficits.

First, we applied correlation analysis to relationships between the selected overall {CAHAI, FM_M}, physical {τ_{max}, MAS, $\dot{\tau}_{peak}$}, somatosensory {FM_P, FM_{LT}, AMDT}, and cognitive {MoCA}impairments, measures of muscle agonist/antagonist coordination {$DiffA_{Tpeak}$, CoA_{Tend}, $DiffA_{Tend}$, CoA_S, $DiffA_{Apk}$}, and coordination (co-articulation) of stabilization and movement control actions {$\Delta\sigma_{stabilize}$, ΔN_{SM}}, (see Table 5.2). Given the limitation of the objective, to evaluate the extent to which specific measures account for variability in CAHAI and FM_M, discussion of correlation results will be limited to significant correlations including either of these two broad measures of function. CAHAI and FM_M were significantly correlated with one another (r = 0.877, p = 0.002, n = 9) indicating that function and impairment are significantly interrelated. CAHAI was also significantly correlated with τ_{max} (r = 0.784, p = 0.012, n = 9), $\dot{\tau}_{peak}$ when reducing isometric flexion torque (r = 0.755, p = 0.019, n = 9), $DiffA_{Tpeak}$ when reducing isometric extension torque (r = 0.683, p = 0.042, n = 9), and $DiffA_{Tend}$ when reducing isometric

extension torque (r = 0.748, p = 0.020, n = 9). These results indicate that motor function is positively correlated to strength, the ability to quickly cease torque production, and the ability to quickly reduce muscle activity. FM_M was also significantly correlated with $\dot{\tau}_{peak}$ when reducing isometric flexion torque (r = 0.802, p = 0.009, n = 9). Thus, motor impairment was significantly correlated with the ability to quickly cease torque production.

Table 5.2: Correlations of upper extremity measures, specific impairment measures, muscle agonist/antagonist coordination measures, and measures of coordination of sequential control actions.

	CAHAI	FM_M	FM_P	FM_{LT}	AMDT	τ_{max}	MAS	MoCA	$\dot{\tau}_{peak}$ (F_R)	$\dot{\tau}_{peak}$ (E_R)	$\dot{\tau}_{peak}$ (R_F)	$\dot{\tau}_{peak}$ (R_E)	DiffA at $\dot{\tau}_{peak}$ (F_R)	DiffA at $\dot{\tau}_{peak}$ (E_R)	DiffA at $\dot{\tau}_{peak}$ (R_F)	DiffA at $\dot{\tau}_{peak}$ (R_E)	CoA after Transition (F_R)	CoA after Transition (E_R)	CoA after Transition (R_E)	CoA after Transition (R_E)	DiffA after Transition (F_R)	DiffA after Transition (E_R)	DiffA after Transition (R_F)	DiffA after Transition (R_E)	ΔN_{SM}	DiffA at A_{PK}	$\Delta\sigma_{stabilize}$	CoA during Stabilization
CAHAI	1																											
FM_M	.88**	1																										
FM_P	.45	.14	1																									
FM_{LT}	.47	.20	.77*	1																								
AMDT	-.46	-.11	-.66	-.54	1																							
τ_{max}	.78*	.58	.42	.68*	-.50	1																						
MAS	-.25	-.57	.19	.01	-.08	-.13	1																					
MoCA	.22	-.09	.53	.53	-.87**	.50	.09	1																				
$\dot{\tau}_{peak}$ (F_R)	.13	.12	-.05	-.41	.10	-.01	.08	-.31	1																			
$\dot{\tau}_{peak}$ (E_R)	-.33	-.17	-.34	-.64	.42	-.73*	-.04	-.70*	.48	1																		
$\dot{\tau}_{peak}$ (R_F)	.76*	.80**	.30	.14	-.19	.54	-.52	.06	.47	-.10	1																	
$\dot{\tau}_{peak}$ (R_E)	.52	.58	-.22	-.46	-.17	.13	-.25	-.11	.55	.31	.58	1																
DiffA at $\dot{\tau}_{peak}$ (F_R)	-.50	-.16	-.42	-.39	.81**	-.65	-.05	-.82**	-.07	.49	-.39	-.29	1															
DiffA at $\dot{\tau}_{peak}$ (E_R)	.41	.35	-.22	.11	.23	.38	.26	-.34	-.05	-.14	-.05	.15	.10	1														
DiffA at $\dot{\tau}_{peak}$ (R_F)	-.43	-.22	-.41	-.38	.67*	-.71*	.10	-.79*	-.19	.64	-.52	-.19	.85**	.26	1													
DiffA at $\dot{\tau}_{peak}$ (R_E)	.68*	.42	.39	.34	-.31	.48	.46	.02	.14	-.14	.19	.31	-.24	.72*	-.03	1												
CoA after Transition (F_R)	.26	.22	.38	.33	-.08	.13	.34	-.06	-.24	-.25	-.15	-.17	.32	.38	.24	.58	1											
CoA after Transition (E_R)	-.46	-.55	.20	.12	.28	-.45	.67*	-.24	-.32	.11	-.67	-.66	.52	.16	.60	.16	.54	1										

CoA after Transition (R_F)	.09	.17	.02	.00	.22	-.16	.32	-.32	-.33	-.03	-.30	-.08	.53	.49	.55	.49	.89**	.59	1								
CoA after Transition (R_E)	-.60	-.62	-.09	-.49	.35	-.81**	.46	-.44	.32	.77*	-.39	-.11	.40	-.28	.56	-.14	-.15	.55	.02	1							
DiffA after Transition (F_R)	-.55	-.19	-.53	-.45	.78*	-.69*	-.11	-.79*	-.12	.51	-.46	-.26	.98**	.08	.86**	-.31	.24	.45	.49	.37	1						
DiffA after Transition (E_R)	.38	.29	-.13	.18	.21	.33	.32	-.33	-.14	-.10	-.11	.06	.11	.98**	.34	.74*	.40	.24	.52	-.18	.08	1					
DiffA after Transition (R_F)	-.39	-.18	-.37	-.38	.64	-.73*	.09	-.76*	-.21	.64	-.47	-.15	.82**	.22	.99**	-.01	.25	.60	.58	.57	.83**	.31	1				
DiffA after Transition (R_E)	.75*	.48	.50	.45	-.42	.60	.37	.14	.18	-.25	.29	.30	-.30	.62	-.19	.96**	.64	.07	.45	-.28	-.38	.61	-.19	1			
ΔN_{SM}	.38	.29	.59	.81**	-.28	.35	-.17	.12	-.48	-.26	-.00	-.41	.08	.18	.13	.32	.53	.26	.32	-.33	.05	.27	.11	.39	1		
DiffA at A_{PK}	-.04	.13	-.40	-.37	-.04	.03	-.60	.00	.47	.24	.33	.46	-.18	-.34	-.33	-.49	-.66	-.81**	-.69*	-.18	-.08	-.47	-.38	-.40	-.38	1	
$\Delta\sigma_{stabilize}$	-.36	-.15	-.50	-.23	.79*	-.41	.05	-.84**	-.06	.47	-.44	-.29	.82**	.49	.85**	-.01	.15	.45	.38	.31	.82**	.51	.78*	-.13	.16	-.16	1
CoA during Stabilization	.09	.08	.07	.00	-.11	-.20	.09	-.30	.11	.46	-.24	.17	.34	.24	.47	.40	.49	.22	.45	.18	.38	.26	.43	.42	.44	-.02	.38	1

CAHAI: 13-item Chedoke Arm and Hand Activity Inventory; FM_M: Upper extremity portion of the Fugl-Meyer Assessment (FMA); FM_P: Proprioception portion of FMA; FM_{LT}: Light touch portion of FMA; AMDT: Arm Movement Detection Test; MAS: Modified Ashworth Scale: MoCA: Montreal Cognitive Assessment; FR: Flex from Relax; ER: Extend from Relax; RF: Relax from Flex; RE: Relax from Extend: PkTqRate: rate of peak change of torque over time; DiffA: Difference Activity; CoA: Co-activity; SM: submovement, APK: peak acceleration. *: significant at p = 0.05; ** significant at p = 0.01

We next used multiple forward regression analyses to quantify the extent to which variation in CAHAI can be explained by our clinical and research measures, {FM_P, FM_{LT}, AMDT, τ_{max}, MAS, MoCA, $\dot{\tau}_{peak}$, $DiffA_{Tpeak}$, CoA_{Tend}, $DiffA_{Tend}$, CoA_S, $DiffA_{Apk,}$ $\Delta\sigma_{stabilize}$, ΔN_{SM}}. Weakness (τ_{max}) accounted for 56% of variance in CAHAI scores [$F_{(1,7)} = 11.195$, $p = 0.012$, Fig. 5.3]. Participants with lower maximal torques, i.e., weaker participants, tended to have lower functional scores. Finally, we used forward regression analyses to quantify the extent to which FM_M could be modeled by our clinical and research measures, {FM_P, FM_{LT}, AMDT, τ_{max}, MAS, MoCA, $\dot{\tau}_{peak}$, $DiffA_{Tpeak}$, CoA_{Tend}, $DiffA_{Tend}$, CoA_S, $DiffA_{Apk,}$ $\Delta\sigma_{stabilize}$, ΔN_{SM}}. The maximal transition rate ($\dot{\tau}_{peak}$) when reducing isometric flexion torque production accounted for 59% of variability in FM_M while the amount of residual muscle activity at the end of this transition (CoA_{Tend}) accounted for a further 17% of variability [$F_{(2,6)} = 13.986$, $p = 0.006$, Fig. 5.3]. Participants who were able to more quickly cease torque and reduce minimal levels of muscle activation when relaxing after torque production tended to have less impairment.

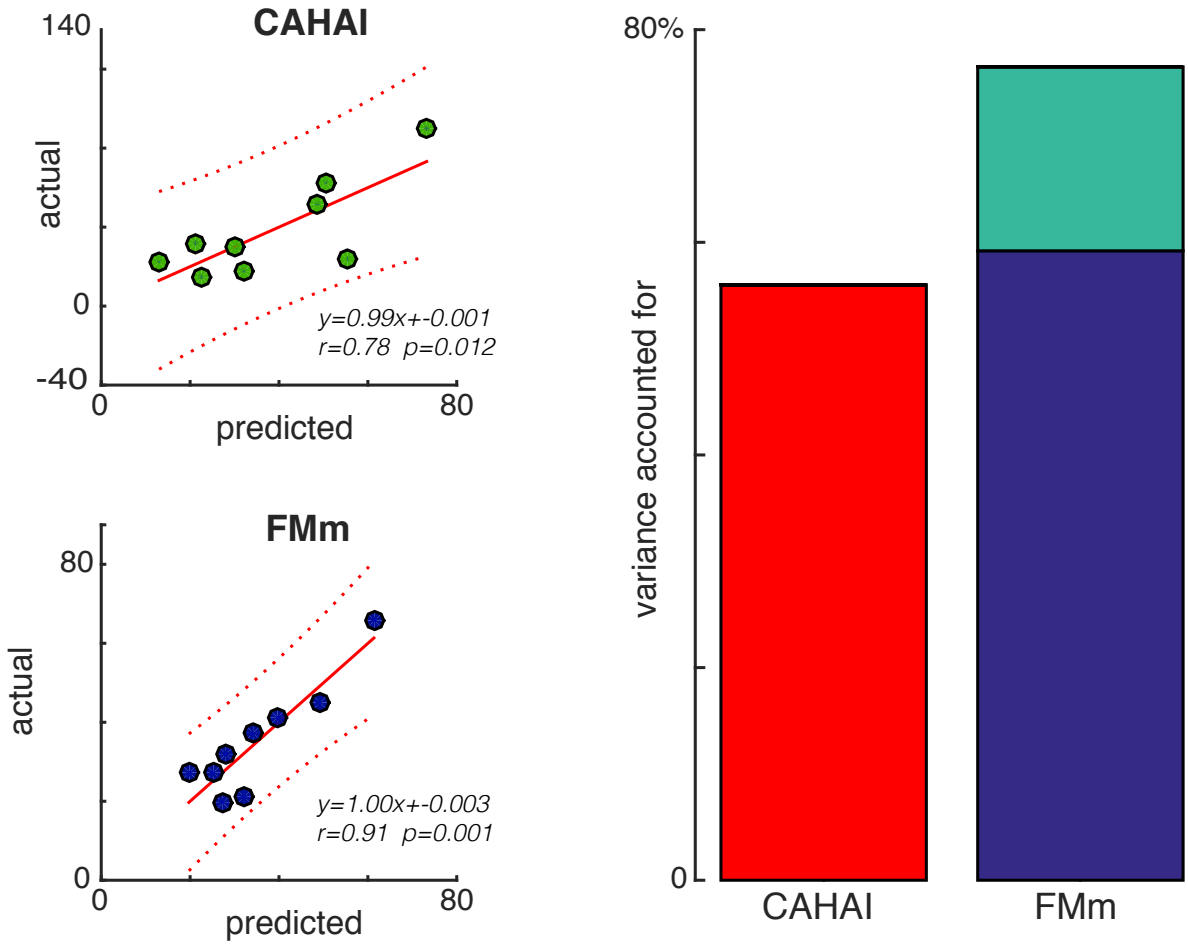

Figure 5.7: Left: Actual vs. model CAHAI (top) and FM_M (bottom) scores. Solid line is regression model, dashed lines are 95% confidence intervals. Right: percent of variance in CAHAI and FM_M scores by model variables. Red bar indicates weakness (τ_{max}), dark blue bar indicates maximal transition rate ($\dot{\tau}_{peak}$) when reducing isometric flexion torque production, teal bar indicates the amount of residual muscle activity at the end of reducing isometric flexion torque (CoA_{Tend}).

Discussion

In this study, we used correlation and forward multiple regression analyses to quantify the extent to which broad measures of function (CAHAI) and impairment (FM_M) of the more-impacted arm after stroke were explained by specific stroke-related deficits including clinical and research measures of physical, somatosensory, and cognitive impairments, as well as measures of coordination of sequential stabilization and

movement control actions, and coordination of agonist/antagonist muscle pairs. We found that the overall measures of post-stroke function (CAHAI) and impairment (FM_M) were significantly correlated with one another. We furthermore observed that upper extremity function (CAHAI) was significantly correlated with weakness and three measures related to the ability to relax the muscles or reduce isometric torque production (DiffA during and after relaxing from extension torque production; $\dot{\tau}_{peak}$ when relaxing from flexion torque production). FM_M was significantly correlated with the rate of torque reduction ($\dot{\tau}_{peak}$ when relaxing from flexion torque production). Forward multiple regression analysis of CAHAI found that of the impairments tested as potential contributing factors, only weakness (τ_{max}) was found to explain significant amounts of variance in CAHAI scores amongst the participant group. Forward multiple regression analysis of FM_M found that two measures relating to reducing isometric torque production and relaxing muscles after isometric torque production ($\dot{\tau}_{peak}$ when relaxing from flexion torque production, CoA after relaxing from flexion torque production) explained significant amounts of variance amongst the participants. Thus, we found that weakness, impairment of the ability to quickly reduce torque production, and impairment of the ability to de-activate muscles quickly contribute to broad impairment and loss of function in the more-impacted upper extremity after stroke.

Neural and muscular causes contributing to impairment in reducing muscle activity, rate of reducing torque

In normal human motor control, the corticospinal tract is thought to be the primary control center for upper extremity movement. Stroke can damage portions of the corticospinal tract. Experiments in non-human primates indicate that when the

corticospinal tract is obliterated, the reticulospinal tract becomes responsible for what upper extremity motor control is recovered (Baker 2011, Zaaimi et al. 2012). Reticulospinal control of upper extremity movement is consistent with the current observations of residual muscle co-activation and slowness in reducing torques.

The differences in the time courses of neurotransmitters in the corticospinal and reticulospinal tracts may explain in part the slowness in reducing muscle activity often observed after stroke. Whereas the corticospinal tract uses glutamate as its primary neurotransmitter (Al Masri 2011), the reticulospinal tract uses monoamine neurotransmitters (Lundy-Eckman 2007). Glutamate is a fast-acting neurotransmitter: it can be released into a synapse, act on its target, and be deactivated in the synapse on sub-millisecond time scales (Danbolt 2001). Thus, under corticospinal drive, an excitatory signal to an alpha motoneuron would be short-lived. Monoamines, however, are slow-acting neurotransmitters that have synaptic actions lasting from tens of milliseconds to many minutes (Lundy-Eckman 2007). Thus, under reticulospinal drive, an excitatory signal to an alpha motoneuron could persist for many minutes.

In addition to having lingering excitatory effects, the reticulospinal tract also does not make direct synapses with inhibitory interneurons in the spinal cord as the corticospinal tract does (Lundberg and Voorhoeve 1962). Through these connections, the corticospinal tract can selectively inhibit alpha motoneurons in non-task-essential muscles, e.g., when the objective is to make an elbow flexion torque, the corticospinal tract can selectively inhibit activity in alpha motoneurons that innervate elbow extensors. The reticulospinal tract does not have this selectivity (Matsuyama et al. 1997, Peterson et al. 1975). Thus, under reticulospinal drive there may simultaneously exist a lack of

targeted inhibition as well as the presence of persistent excitatory neurotransmitters. This combination could lead to elevated levels of co-activation observed after stroke.

Factors contributing to weakness after stroke

Weakness is consistently found to correlate significantly with function and impairment after stroke (Ada et al. 2006, Kamper et al. 2006, Harris and Eng 2007, Chapter 3, Chapter 4), however, producing torque about a joint (a common measure of strength) requires that muscle activity be coordinated in time and magnitude. Trombly and colleagues (1992) observed that, after stroke, participants used a greater percentage of their maximal muscle activation to complete a targeted reaching task with the more-affected arm than with the less-affected arm. Wagner and colleagues (2007) noted a similar phenomenon in a study comparing targeted reaching in the more-affected arm of SP in the acute phase (less than two weeks since stroke) and the subacute phase (approximately four months after stroke) of recovery. They found that in the early testing, SP used a large percentage of their available range of muscle activation to complete the targeted reaching task. The amount of activation tended to decrease as recovery progressed from acute to sub-acute, but the amount of activation used was still greatly elevated compared with NI controls suggesting that there was less "wasted" activity after recovery, but that control and execution of motor tasks did not return to "normal" at a muscular level.

Some amount of co-activation observed after stroke may be a strategic compensation for impairment in quickly reducing muscle activity in task-agonist muscles. If one cannot quickly reduce activity in a contracting, torque-producing muscle

(see Fig. 5.2A), one method for reducing torque about a joint would be to activate the opposing muscle, i.e., co-activate (See Fig. 5.3A). The force applied by the task-antagonist muscle would reduce the torque measured at that joint. Indeed, when attempting to relax from isometric extension torque production (Fig. 5.3), participants in this study showed high levels of co-activation as well as residual extensor activation. Given that net torque is the sum of all torques applied at the joint, this strategy will reduce torque about the joint, but it is inefficient and can contribute to measured weakness.

In addition to this potentially-compensatory control strategy, descending drive from the reticulospinal tract is only 20% as strong as descending drive from the corticospinal tract (Riddle et al. 2009), and thus it is more difficult to recruit the large numbers of motor units required to produce large forces. Additionally, these neural changes can lead to remodeling at the muscular level that can also impair force production. Post-stroke muscular changes that negatively impact isometric force production capacity (and therefore increase weakness) include decreases in anatomical cross-sectional area of the more-impacted arm (Berenpas et al. 2016, Ryan et al. 2002), decreases in lean muscle mass on the more-impacted side (English et al. 2010), and decreases in the number of contractile elements in the more-impacted muscles after stroke (Hafer-Macko et al. 2008). Thus, weakness observed after stroke is likely the combined product of changes in neural control and muscular remodeling.

Better understanding of causes of impairment and lost function is important for designing interventions

This work relates an array of measures of specific impairments to broad clinical measures that are often used to track and quantify motor recovery after stroke. The finding that weakness contributes to motor impairment and decreased motor function after stroke (Ada et al. 2006, Kamper et al. 2006, Harris and Eng 2007) is not novel. However, this work adds to understanding of the underlying causes of weakness, and suggests that weakness is, in part, a product of deficits of coordinated neuromotor control in addition to being the product of decreased force production capacity of muscles themselves.

Knowledge of the characteristics underlying broad measures of motor deficits is useful for research and design of clinical interventions. Better understanding of the underlying factors contributing to motor impairment and lost motor function after stroke is necessary to create targeted, hypothesis-driven intervention protocols. A challenge such as reducing muscle activation, given the neural contributions to increased excitability of alpha motoneurons, may require pharmaceutical intervention with anti-spasticity agents which may reduce persistent muscle tone (Olvey et al. 2010, Pandyan et al. 2002). If such an intervention is not feasible, knowledge of the phenomena underlying observed motor deficits may also be used to help therapists set appropriate expectations and design compensatory strategies that may help survivors of stroke to achieve their movement objectives to the extent possible. For instance, if one wishes to release grasp of an object, but cannot quickly relax the flexors or activate the extensors (and indeed, may experience *increased flexion* when attempting to volitionally extend the fingers, cf.

Kamper et al. 2003), one strategy might be to stabilize the object against a stable surface and allow the muscles to relax over the course of several seconds before attempting to remove the hand.

This study is limited in the number of participants (n = 9), which decreases detection power of the statistical tests. The fact that there is good agreement across the findings of this study and that of Chapter 3 (which had more participants) does support the validity of the results in this small sample.

Conclusion

The present study provides an analysis of the extent to which specific, stroke related deficits contribute to broad measures of impairment and function in the more-impacted upper extremity. We found that significant variance in CAHAI scores was accounted for by weakness, and that significant variance in FM_M scores was accounted for by the maximal rate at which survivors of stroke could reduce torque and the amount of co-activation present after attempting to relax from torque production. We interpret this to mean that while weakness is an important contributor to loss of function after stroke, we must also consider the underlying causes of weakness, including deficits in control and muscle mechanical function. Knowledge of the mechanisms underlying observed clinical deficits is necessary to design better interventions to treat motor-limitations post stroke.

CHAPTER 6: CONCLUSIONS, LIMITATION, AND FUTURE DIRECTIONS

Conclusions

We used measures of elbow torque, muscle activity, and kinematics in survivors of stroke (SP) compared to neurologically-intact (NI) controls to quantify deficits in three areas: torque production, agonist/antagonist muscle coordination, and control and sequential coordination of stabilization and movement control actions at the elbow. In chapter 3, we found that in comparison to NI, SP showed deficits in coordinating the timing and magnitude of elbow flexor and extensor activation while creating and ceasing flexion and extension torques. Upper extremity impairment was found to be significantly correlated with weakness, and upper extremity function was found to be significantly related to weakness and coordination deficits measured when relaxing immediately after sustained torque production. These findings suggest that coordination of agonist/antagonist muscle pairs may contribute significantly – above and beyond the impact of simple measured weakness – to deficits of function after stroke. In chapter 4, we found that SP showed deficits in control and sequential coordination of stabilization and movement control actions compared to NI. In addition, we found that differential deficits in control of stabilization and movement within the SP group were well explained by impairments in proprioception. Specifically, SP with intact proprioception were able to stabilize the elbow against a perturbation with less variability in position than those SP whose proprioception was measured to be impaired. However, SP with intact proprioception actually performed worse during movement than SP with impaired proprioception: those with *intact* proprioception required more submovements to

complete a targeted elbow flexion task than did SP with *impaired* proprioception. These findings suggest that stroke-related deficits in proprioception impair stabilization control, but may – counterintuitively – facilitate smoother movements after stroke. Additionally, in Chapter 4, we observed that SP were unable to reduce the amount of co-activation about the elbow even when there was no functional reason to have elevated co-activation, unlike NI who decreased elbow co-activation when they were not required to stabilize the elbow. Forward multiple regression analyses using measures of impaired control of movement and stabilization actions in SP and clinical measures of specific impairments as potential model variables found that only weakness accounted for significant variability in upper extremity motor function, and came the closest to explaining significant variability in upper extremity impairment. This suggests that stroke-related impairments in specific control actions (i.e., movement and stabilization) are not as important to explaining broad deficits as are measures of simple physical deficit, such as weakness. In chapter 5, we found that significant variance in scores of function were explained by weakness, and that significant variance in scores of impairment were accounted for by the rate at which SP could reduce torque production and the amount of co-activation that was present at the end of torque-reduction transitions.

Across the three studies we found consistent indications that weakness is an important factor contributing to loss of upper extremity motor function and upper extremity motor impairment after stroke. Additionally, stroke-related impairments in coordinating activity in agonist/antagonist muscle pairs – especially when relaxing from torque production – was a consistent finding across all three chapters. In Chapter 3, the amount of net muscle activity remaining after reducing torque was included as a

significant factor in the model of function and in Chapter 5, we observed that the amount of co-activation present after reducing torque was included as a significant factor in the model of impairment. While measures of agonist/antagonist coordination were not included in the models of function and impairment in Chapter 4, we did observe elevated residual co-activation when it was not necessary (i.e., prior to flexion movements in which the participant had been relaxing prior to movement). We conclude dis-coordinated activation of agonist/antagonist muscle pairs, including residual activation, are important contributors to observed weakness, slowness, and difficulty in reducing torques observed after stroke.

Furthermore, the results show that proprioception is a key factor underlying observed differential impacts of stroke on stabilization and movement control actions (Chapter 4). Prior explanations of these differential deficits have found that laterality (i.e., whether the right or left arm was more-impacted by stroke) coincided with the type of deficit observed: those who were more-impacted in the right arm showed greater deficits during movement control, while those who were more-impacted in the left arm showed greater deficits during stabilization control (Schaefer et al. 2009, Schaefer et al. 2011, Mani et al. 2013). Recent findings by Kinzie and colleagues (2016) indicate that proprioceptive deficits after stroke are lateralized in a manner consistent with the findings of Schaefer, Mani and colleagues.

The findings from these three studies have broad scientific and clinical impact. First, the finding of persistent, non-task relevant residual co-activation (Chapters 4 and 5) demonstrate that one barrier to restoration of motor function after stroke is lost ability to fully relax muscles after use. Even low levels of persistent muscle activation can have

insidious impacts in motor control, including increased sensitivity of stretch reflexes and increased mechanical resistance about the joint, even in those with intact descending motor control (Burne et al 2005). However, in those with impairments in descending control, including weak descending drive, increased stretch reflex activity and joint impedance would be more difficult to cope with. Lost descending control from the corticospinal tract control is likely subsumed by the reticulospinal system (Baker 2011, Zaaimi et al. 2012). The reticulospinal tract has much less fractionation and flexibility than does the corticospinal tract, which makes it less able to compensate for these positive symptoms of disordered motor control (Matsuyama et al. 1997, Peterson et al. 1975). Additionally, the reticulospinal tract likely contributes to the higher levels of persistent muscle activation in that it both has decreased ability to drive inhibition of alpha motoneurons in the spinal cord (Lundberg and Voorhoeve 1962) and it uses slow-acting excitatory neurotransmitters that can linger in the synapse for minutes (Lundy-Eckman 2007). Finally, these studies indicate that stroke may be a good model for studying the impact of proprioception on individual movement control actions.

Limitations

Stroke can cause a broad range of deficits in movement (Bobath 1990, Ghika 2005), somatosensation (Brain 1956), and specific components of proprioception (Kinzie et al. 2016). The wide variability of motor and sensory impairments may limit applicability of our findings. In addition, these studies are also limited in that they examine muscle activity, torque production, and movement only at the elbow. While this choice was made to allow us to get closer to the mechanisms underlying coordination of

agonist/antagonist muscle pairs and sequential stabilization and movement control actions after stroke, the extent to which our findings apply to multi-joint movements remains an open question.

Limitations were introduced in our electromyography (EMG) signals when the data were normalized to maximal isometric volitional contractions (MVICs). First, given that SP have reduced descending drive (cf. Riddle et al. 2009), it is possible that the maximal *volitional* contraction does not completely reflect the maximal *possible* contraction that the muscle can achieve. Furthermore, values were normalized to the measured MVIC value for each participant in order to compare across participants and across groups. While this was necessary to achieve our experimental objectives, it is likely that NI participants have higher levels of raw MVIC than do SP. Thus, when the processed EMG values are divided by smaller numbers (likely in the SP group), a given raw value would account for a larger percentage of the maximal range than the same raw value divided by a larger number (such as in the NI group).

Furthermore, the amount of EMG activity recorded is a good indicator of the amount of activity in that muscle, but not the amount of force being produced by that muscle (Lieber 2002). Assuming the amount of observed activity in a muscle is held constant, the amount of force produced by the muscle would be smaller if the muscle was held in a shortened position, or if it was actively shortening in a concentric contraction. Conversely, the same amount of measured activation would be associated with greater levels of force production if the muscle is held in a lengthened position, or is actively lengthening in an eccentric contraction. Given the mechanics of the elbow agonist/antagonist muscle pairs, when one muscle is shortened or shortening, the

opposing muscle is lengthened or lengthening. Thus, while the experimental measures of CoA and DiffA used throughout these studies can effectively relate the amount of normalized muscle activity in a given time window, they cannot accurately reflect the forces being created by those muscles.

Future Directions

Reducing persistent muscle activity may improve function after stroke

Consistent with our observations of persistent, low-level muscle activation in the survivors of stroke, several other research groups have observed elevated muscle activity in surface EMG (Burn et al. 2005) and intramuscular recordings of EMG (Chang et al. 2013, Mottram et al. 2009, Mottram et al. 2010) in the more-impacted muscles of survivors of stroke. Currently, treatments that can effectively reduce muscle tone include targeted botulinum toxin injections, and oral or intrathecal baclofen (Olvey et al. 2010, Pandyan et al. 2002). While these treatments can be effective for reducing overall muscle tone in spastic muscle, they can be expensive, invasive, and may not work for everyone (cf. Yoon et al. 2017).

One potential, non-invasive approach to reduction of muscle tone and preservation of force production after stroke may be dietary supplementation of taurine. Taurine has been demonstrated to improve calcium sequestration in neurons (Foos and Wu 2002) and in skeletal muscle (Dutka et al. 2014, Goodman et al. 2009). Indeed, when neurons are subjected to persistent excitation (such as prolonged glutamate exposure), their ability to regulate intracellular calcium transport can be impaired which can lead to excitotoxicity (Foos and Wu 2002). While alpha motoneurons are not experiencing

persistent glutamate excitation, they are likely under prolonged excitatory effects of monoamine neurotransmitters (Lundy-Eckman 2007). Improved ability to sequester calcium in the endoplasmic reticulum could potentially allow these motoneurons to de-activate more quickly or effectively. Additionally, studies in human skeletal muscle fiber preparations have demonstrated that increased levels of intramuscular taurine increase the rate of calcium accumulation in the sarcoplasmic reticulum, but not the total quantity of calcium sequestered (Dutka et al. 2014). Thus, the muscle can de-activate more quickly when greater levels of taurine are present. Finally, Goodman and colleagues (2009) used a rat model to demonstrate that dietary taurine supplementation increased intramuscular taurine concentrations. This led to increased force production in the muscles during isometric twitch stimulation and tetanic force production, as well as retained force capacity after repeated stimulation compared with controls who were not given taurine supplementation. Faster, more complete de-activation of motoneurons and muscles, as well as increased and preserved force capacity would be beneficial to survivors of stroke.

Use computational modeling to tease apart neural and muscular contributions to motor dysfunction after stroke

The neural system and muscles are intimately linked, and both can remodel based on changes in one other. Thus, it is difficult to quantify the extent to which deficits in movement are caused by lost descending neural control and the extent to which these deficits are explained by physical changes in the mechanical and contractile properties of muscle. Computational modeling could be used to tease apart the contributions of neural deficits and those of remodeled muscle tissues to the abnormal movements observed after stroke. The datasets gathered in Aim 2 of this Dissertation include electromyographic and

kinematic data of survivors of stroke performing movement and stabilization tasks about a single joint. These data could be used to create computational neuro-musculo-skeletal models (c.f. Zajac and Winters 1990) that can help disambiguate questions of the extent to which motor deficits after stroke are due to changes in descending control and the extent to which they are the result of the mechanical constraints of remodeled muscle and connective tissues.

Rehabilitation methodologies designed to strengthen and refine reticulospinal control may improve outcomes after stroke

More severely impaired survivors of stroke have likely lost more corticospinal control than those who are less impaired. This lost control is supplanted by the reticulospinal tract, which has important limitations when compared with corticospinal control of movement including weaker, more diffuse connections to alpha motoneurons (Matsuyama et al. 1997, Peterson et al. 1975), lack of connections with inhibitory interneurons, and use of slow-acting neurotransmitters rather than fast-acting neurotransmitters (Lundy-Eckman 2007). The extent to which motor function can potentially be restored by the reticulospinal system and the amount and types of training required to do so remains an open question. Experiments in non-human primate models indicate that in the absence of corticospinal control, reticulospinal connections can be strengthened with use (Zaaimi et al. 2012). Thus, it may be useful to observe animal models to gain an understanding of the limitations of control of the reticulospinal system. For example, when Zaaimi and colleagues severed one side of the corticospinal tract in non-human primates, the animals could no longer extend the fingers of the more-

impacted forepaw, but could use the more-impacted forepaw to climb bars in the cage (2012).

Currently, there is at least one rehabilitation protocol, Arm BASIS training, designed to restore movement in the more-impacted limb of severely-impacted stroke survivors (Platz et al. 2005). In this protocol, a clinician assists the patient in moving individual joints in the more-impacted arm throughout the volitional range of motion. During the first phase, the therapist supports the arm against gravity, and during the second phase the patient learns to make the same series of isolated movements while also compensating for gravity. During the third phase of training, patients are taught to combine the individual degrees of freedom into multi-joint movements. Arm BASIS training has been found to enhance selective motor control in the more-impacted arm of severely-impaired survivors of stroke (Platz et al. 2005). Given the protocol and the target population for this therapy, it appears that Arm BASIS training is directed at improving reticulospinal control of arm movement. Also, given the highly intensive nature of Arm BASIS training, this intervention protocol could potentially benefit from translation to a robotic therapy so that severely impaired patients can receive increased dosages without having to utilize as much therapist time.

Examine role of proprioception on segmentation of multi-joint movements

Increased movement segmentation, also called submovements, in multi-joint movements after stroke has been noted extensively in the literature (Krebbs et al. 1999, Cirstea and Levin 2000, McCrea et al. 2005, Rohrer et al. 2002, Rohrer et al. 2004, Dipietro et al. 2009). However, we are not aware of any study explicitly examining

impact of stroke-related proprioceptive deficits on segmentation of multi-joint movements after stroke. In Chapter 4, impairments in proprioception after stroke were associated with degradation of stabilization control, but less segmented movement control. Thus, the presence or absence of proprioceptive deficits can explain differential impairment in limb stabilization and movement control actions in a single joint, at least in part. However, deficits observed in the one-joint stabilization and point-to-point elbow flexion task do not necessarily relate directly to measures of function or impairment after stroke. We believe this may be due to the fact that the types of actions tested in our selected measures of function and impairment, which require coordination of multiple limb segments in order to complete, are dissimilar from single-joint tasks such as the one tested in Chapter 4 which only tests the arm about a single degree-of-freedom. Furthermore, proprioception itself is made up of a multitude of signals encoding position and movement by sensors located in the skin, muscles and joints (Proske and Gandevia 2012). The clinical measure of proprioception used here is a coarse evaluation of proprioceptive acuity (DeGowin et al. 1987, Epstein et al, 2008). Future experiments designed to specifically quantify the role of proprioception in differential impairment of stabilization and movement control actions could use more explicit, ratiometric measures of different components of proprioception (Hillier et al. 2015), in addition to the ratiometric measure of kinesthesia used here. These limitations motivate a study to quantify the impact of specific components of proprioceptive impairments on movement segmentation in multi-joint reaching.

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APPENDIX A: EFFECT OF BOTULINUM TOXIN ON MOVEMENT

Introduction

This Appendix describes the rationale for excluding survivors of stroke who had received Botox (BTX) injections in upper extremity muscles from the analyses of Chapter 4 (Aim 2). Although these individuals were originally included in the experiments of Chapter 3 (Aim 1), we shall show through kinematic analyses that stroke survivors who had received Botox (the BTX group) injections performed the elbow flexion task in a manner that was markedly different from the performances of stroke survivors not receiving anti-spasticity treatment (the SP group).

Approach and Results

To consider whether or not the performance of BTX participants was consistent with performance of the SP group, we first considered the percentage of good trials performed by each group:

NI: 97.6% good trials

SP: 95.6% good trials

BTX: 72.7% good trials

Participants in the BTX group have a notably smaller percentage of good trials than NI and SP groups.

Next, we normalized each participant's reach kinematics to their individual target distance (i.e., each participant's elbow displacement time series were divided by their individual target distance). This allowed all participants to be judged against their own

performance capability. Then, we performed rank-transformation and inverse normal transforms on the target-normalized kinematic data; this approach, which reflects the final form of the data analyses reported in Chapters 3 and 4, facilitates robust tests of whether or not the groups are similar in kinematic performance.

For the following comparisons, we chose to combine variables across different trial types to focus more broadly on performance amongst groups. Error bars indicate 95% confidence intervals on the mean of the RT-INT transformed data.

Fig A1 compares RT-INT execution times. Compared with the SP and NI groups, the BTX group takes significantly longer to complete the flexion movement.

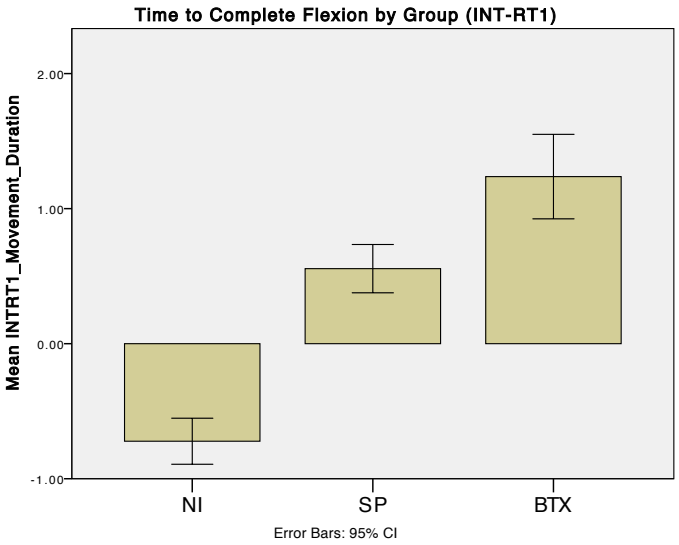

Figure A1: Group mean and standard error of INT-RT1 transformed time to complete flexion movement. NI: neurologically intact control, SP: survivors of stroke not receiving botulinum toxin injections; BTX: survivors of stroke receiving botulinum toxin injections

Figure A2 compares RT-INT submovement counts. Compared with the SP and NI groups, the BTX group require significantly more submovements.

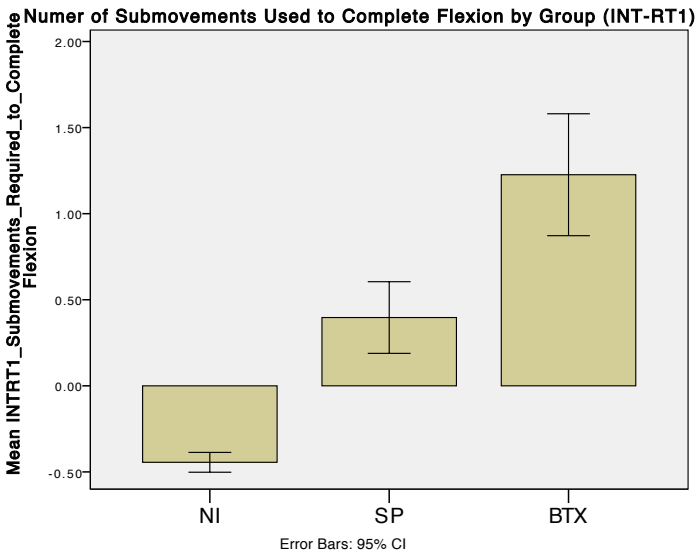

Figure A2: Group mean and standard error of INT-RT1 transformed number of submovements required to complete flexion task. NI: neurologically intact control, SP: survivors of stroke not receiving botulinum toxin injections; BTX: survivors of stroke receiving botulinum toxin injections

Figure A3 compares RT-INT movement speed. The BTX group made movements that were considerably slower than those made by the SP and NI groups.

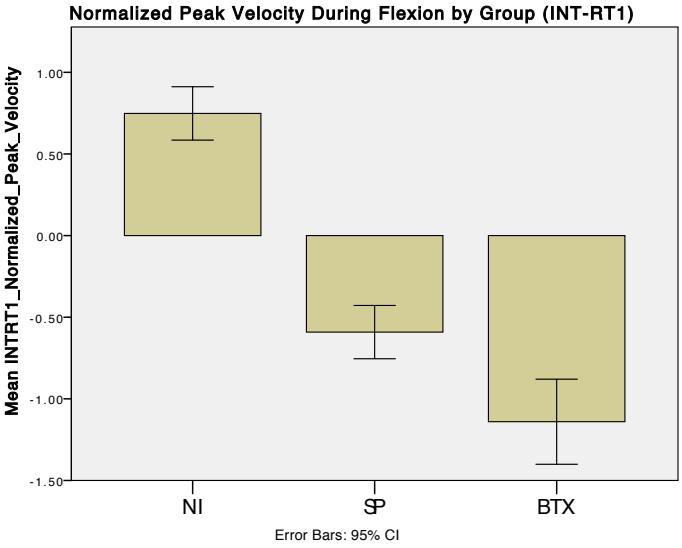

Figure A3: Group mean and standard error of INT-RT1 transformed position error prior to movement. . NI: neurologically intact control, SP: survivors of stroke not receiving botulinum toxin injections; BTX: surviviors of stroke receiving botulinum toxin injections

Figure A4 compares RT-INT extents of first submovements. The BTX group made significantly shorter first submovements than did the SP and NI groups.

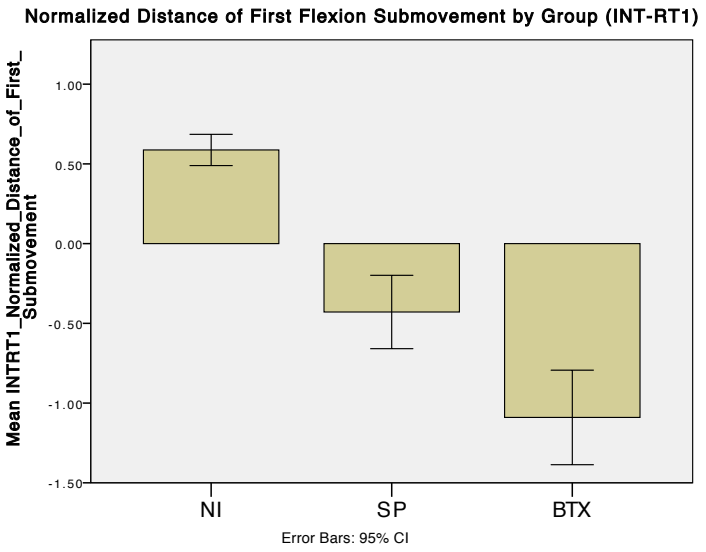

Figure A4: Group mean and standard error of INT-RT1 normalized distance of first flexion submovement during flexion task. NI: neurologically intact control, SP: survivors of stroke not receiving botulinum toxin injections; BTX: survivors of stroke receiving botulinum toxin injections

Figure A5 compares RT-INT target capture errors at the end of first submovements. The BTX group's first submovements exhibited significantly greater undershoot error at the end of the first submovement than did the SP and NI groups.

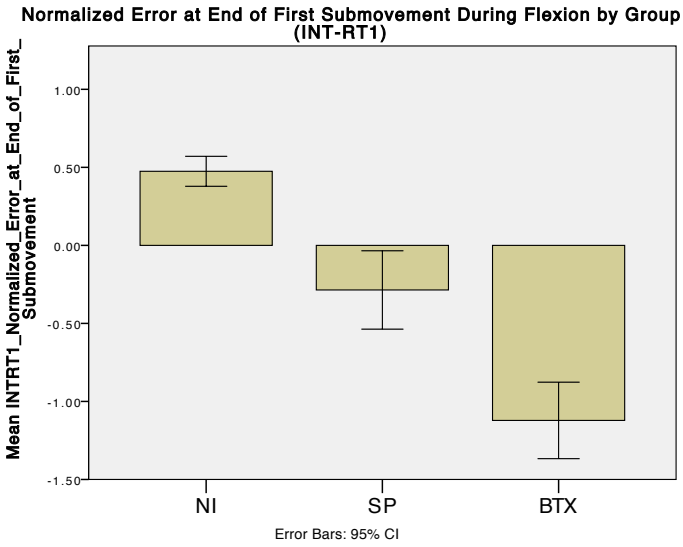

Figure A5: Group mean and standard error of INT-RT1 transformed normalized movement error at end of first flexion submovement. NI: neurologically intact control, SP: survivors of stroke not receiving botulinum toxin injections; BTX: survivors of stroke receiving botulinum toxin injections

Conclusion

The BTX participants differed significantly from the SP group in nearly every kinematic performance measure during reaching. I conclude therefore that the two subgroups of stroke survivors represent distinct populations when it comes to the kinematics of reaching, and that it does not make sense to combine the two stroke survivor groups in the analyses of movement control of Aim 2 (Chapter 4). Combining the two groups would introduce unwanted variability, which would reduce the statistical power of the Aim 2 study (Chapter 4) by "swamping out" meaningful stroke-dependent differences in sensorimotor control of limb movement and holding still.